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COMMUNICATIONS

TWO CASES OF VISIBLE EMBOLI IN RETINAL ARTERIES

With a Histological Study in one case

BY

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1.—Case Reports (G.C.P. and L.H.S)

IN view of their rarity it seemed worth while recording the ophthalmoscopic appearances of two cases in which actual emboli could be seen in retinal arteries. Subsidiary matters of interest were the reactions of neighbouring vessels to the emboli and to vasodilator drugs.

CASE 1.—At 8.30 a.m., on May 26, 1941, when going on duty, Sister K. H., of Horton Hospital, suddenly noticed a complete "black-out" of her left eye. She rubbed her eye with her hand, and in about two minutes the lower half of the field of vision began to clear. After about 20 minutes this half of the field was approximately normal; but the upper half was still absent. Next day about 6.50 p.m. her eyes were examined. At that time the R. vision was 6/5 and L. vision 6/9. The left pupil reacted sluggishly to light. The retina in the lower half was white and opaque. The inferior temporal branch of the central artery was contracted from the disc to just above the second fork of the vessel. (Fig. 1). The upper branch of the first fork running beneath the macula was also in a state of contraction. At the bifurcation of the second fork (Figs 1 and 2) a white mass could be seen in the lumen and apparently including the wall of the vessel, so that the width of the mass appeared to be a little wider than the calibre of the vessel. The artery just above the fork was dilated, as were also the two branches of the fork for about 1/4 disc breadth below—after that the branches

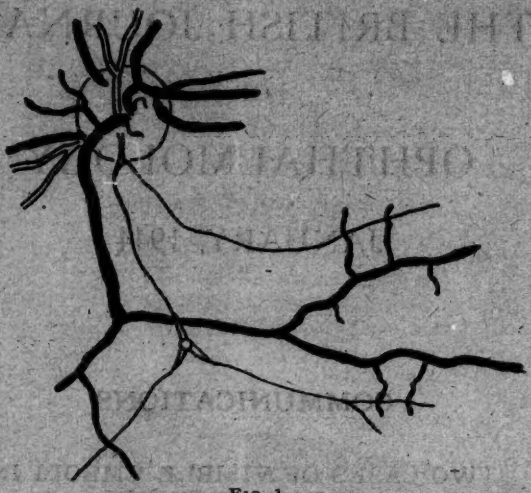

FIG. 1.

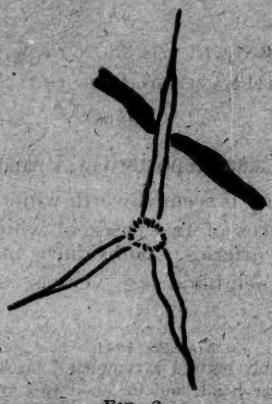

FIG. 2.

were contracted. It was concluded that the white mass was an embolus lodged in the vessel. The field was contracted generally, especially in the upper nasal quadrant, where the boundary approached the fixation point. (Fig. 3).

Although rather a long interval had elapsed a capsule of amyl nitrite was administered. A subconjunctival injection of 40 mg. acetylcholine was made followed by 20 mg. of mecholyl (acetyl-beta-methyl-choline) subcutaneously. There was marked general upset within two minutes of the mecholyl injection. The pulse raced, marked vasodilation occurred, and the systolic blood-pressure dropped from 140 mm. Hg to 120 mm., rising again to 150 mm. in 20 minutes. Diastolic pressure was unchanged.

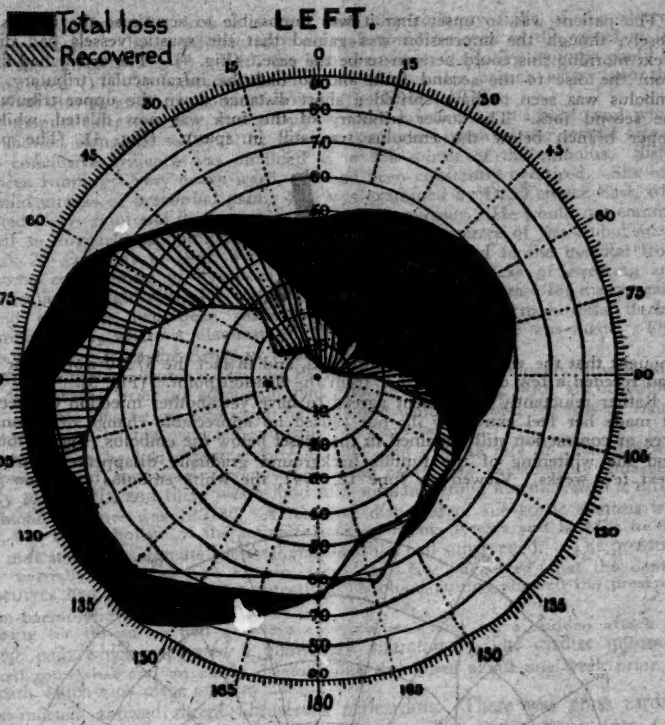

FIG. 3.

FIG. 4.

The patient was so upset that it was impossible to scrutinise the fundus very closely, though the impression was gained that the spastic vessels had dilated. Next morning this could be seen to be the case. (Fig. 4). The artery had dilated from the disc to the second fork, and so had the inframacular tributary. The embolus was seen to have shifted a short distance down the upper tributary of the second fork. The lower tributary of the fork was now dilated, while the upper branch below the embolus was still in spasm. (Fig. 4). The patient

FIG. 6.

thought that the visual field had improved, and in fact the 5/330 isopter for white had receded a few degrees further from the fixation point. (Fig. 3).

Rather reluctantly the patient agreed to have yet another injection of mecholyl. It made her feel extremely ill; but caused no appreciable change of vision. An area of contraction still remained in the vessel below the embolus (Fig. 5); but this and the whitening of the fundus background gradually disappeared during the next few weeks. Viewed on June 12, 1941, the white embolus could no longer

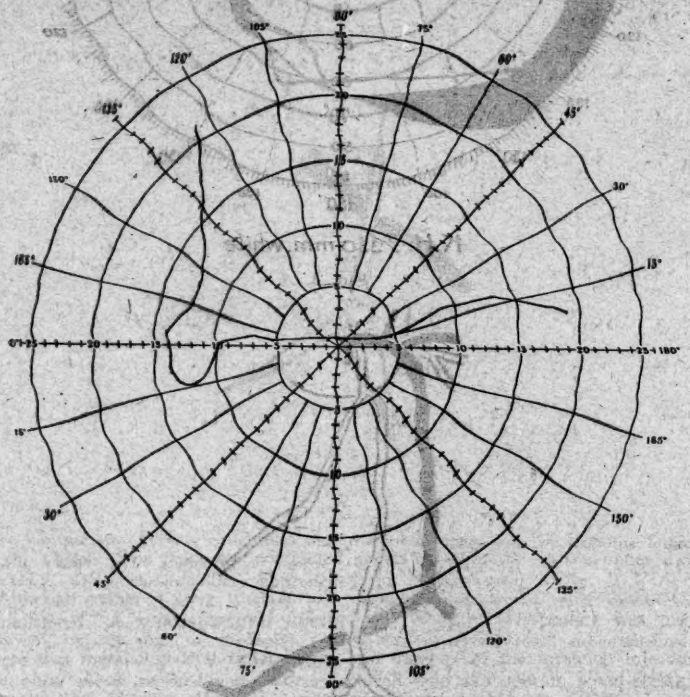

FIG. 7.

be seen and the vessel looked normal with the ordinary light of the electric ophthalmoscope. Using red-free light a break could be seen in the vessel at the site of the embolus (Fig. 6). With the Bjerrum screen a relative scotoma could be demonstrated (Fig. 7) corresponding to the inframacular branch artery and this shaded off into an absolute scotoma above. (See Bedell, 1937).

Six months later the disc was atrophic in the infralateral quadrant; and white lines showed along the walls of the inferior temporal branch of the central artery.

No conclusive evidence was obtained as to the source of the embolus. Sister had been running a very heavy ward, and had been constantly overtired. She had had mild attacks of precordial pain. She was examined by Dr. Terence East, who reported a very faint and inconstant mitral systolic murmur. He would not commit himself to any definite opinion that the heart was the source of the embolism.

CASE 2.—On May 6, 1942, a man aged 30 was admitted to the hospital from his home complaining of dyspnoea on slight exertion; attacks of sweating and blindness in the right eye. He was aware that he had heart disease for many years, but no diagnosis had been made until he was admitted to hospital during December, 1941, where a diagnosis of congenital heart disease was made. This led to discharge from the Army in February, 1942.

Since a complete dental extraction he had apparently felt vaguely unwell, and for a few weeks prior to admission had attacks of sweating with an occasional rigor. On the day before admission he collapsed while at work, the loss of vision of the right eye having occurred suddenly five days before.

On admission he had a temperature of 101° and a pulse rate of 100. He was orthopnoeic and moderately cyanosed. The heart was considerably enlarged, mainly to the left, and there was a loud mid-sternal systolic murmur with a thrill. The blood pressure was 120/80. A tentative diagnosis of sub-aortic stenosis was made, but the embolism of the retinal artery, swinging pyrexia and R.B.C's in the urine indicated that subacute bacterial endo-carditis had supervened. The presence of a partially extruded sequestrum from the jaw suggested that the dental manoeuvres had precipitated this infection. A blood culture showed the presence of non-haemolytic streptococci.

During his illness he had a severe epistaxis and later on a sudden attack of thoracic pain which suggested a pulmonary infarction. The cardiac murmurs changed somewhat and an aortic diastolic one developed about one week prior to his death which took place on May 22.

Post-mortem showed recent fibroserous pericarditis. There was gross cardiac enlargement affecting primarily the left ventricle. The aortic cusps were surmounted by very large greenish friable vegetations. There was an abnormal 4th cusp present. There was an aneurysm of one sinus of Valsalva, the endocardium of which was largely involved by the infection. The aorta was hypoplastic and a thickened fibrous band represented the ductus arteriosus. There was a typical septic spleen, some nutmeg change in the liver, and an early embolic nephritis. There was a bilateral effusion in the chest. The lungs showed hypostatic congestion with considerable oedema of the upper and middle zones.

Dr. W. Bridgen summarised the case as consistent with subacute bacterial endocarditis superimposed on an unusual congenital cardiac abnormality.

From the ophthalmic point of view the main interest lay in sudden loss of central vision in the right eye on May 1, 1942. Ophthalmoscopic examination showed a white mass lodged in the temporal branch of the first lower fork of the central artery just inside the disc margin. (Fig. 8). There was an area of retinal pallor in the region supplied by the branch. The circulation was not completely obstructed as cattle-truck movement of the blood-column could be seen below the macula. (Fig. 8). The arteries generally, distal to the embolus, were extremely constricted.

A subconjunctival injection of 40 mg. acetylcholine was made, followed by 20 mg. of mecholyl. The blood-pressure, which had been 118/78 mms. Hg. fell to 90/68 mms. Hg. After a further 20 mgs. of mecholyl it read 78/60 mms. Hg. The patient felt very hot and vomited, so he was given atropine gr. 1/100. Symptoms at once disappeared and the blood pressure rose to 110/80 mms. Hg.

Ophthalmoscopically the artery below the embolus was seen to dilate for a short part of its length immediately below the block following the acetylcholine.

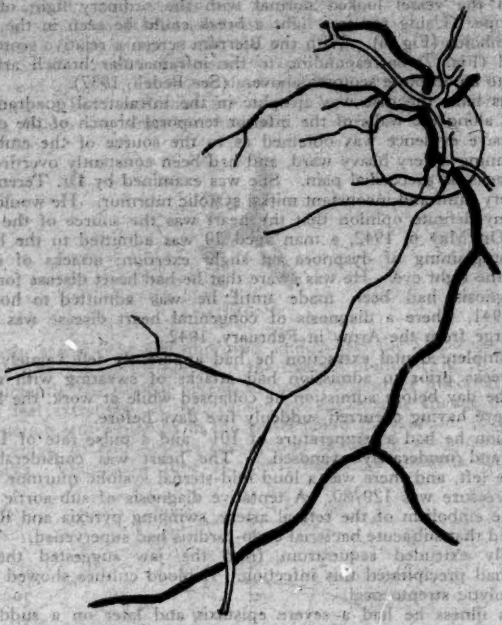

FIG. 9.

FIG. 10.

After the mecholyl the peripheral end of the vessel began to dilate, and the proximal dilatation below the block extended a little peripherally. (Fig. 9). Next day the vessel was still more dilated, the proximal and distal dilatations, being separated by a length of vessel in spasm about 1 disc diameter in length. (Fig. 10).

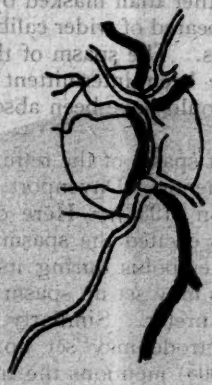

FIG. 11

By May 14, 1942, the vessel was uniformly dilated (Fig. 11); the patient said his vision was improved, though his general condition precluded accurate objective testing. He had symptoms of a lung embolism on May 11, 1942. After his death on May 22, 1942, his right eye was removed for histological examination.

Discussion

Numerous points for consideration arose from these cases.

(*a*) Was the white patch in the vessel in Case 1 an embolus? It was difficult to see what else it could be, and its appearance was identical with the patch in Case 2—which was definitely an embolus. Werner (1913) reports a case where " just below the disc the inferior temporal artery was blocked by an oval glistening-white object, below which the vessel was thread-like, while above this part it was normal in size." The white object was $1\frac{1}{2}$ times the normal diameter of the vessel, the apparent enlargement probably being due to opacity in the vessel wall surrounding the embolus. Paton (1933) described a similar opacity with an apparent diameter of 2 mm.

(*b*) In case 1 we thought the sequence of events to be as follows:—

In the first instance the embolus blocked the main trunk of the central artery causing the complete black-out initially noted. Sister rubbed her eye with her hand, causing the embolus to move on

to the second fork of the inferior temporal branch. The lower visual field cleared while the onward passage of the embolus set up spasm of the branch and its tributaries, presumably by the mechanical stimulation. We think the thread-like vessels must have been in spasm, rather than masked by oedema, or it is difficult to see why they appeared of wider calibre after the administration of vasodilator drugs. The spasm of the inframacular branch in this case must have been intermittent or incomplete, or the whole of the scotoma would have been absolute instead of relative near the fixation point.

There is evidence that spasm of the retinal vessels is a comparatively common phenomenon, (Davenport (1931), Griffith (1931), Traquair (1933), Minton (1936)). Here one would suppose the passage of the embolus excited the spasm mechanically, causing the vessel to grip the embolus during its passage, in the same way that a renal calculus may set up spasm and be gripped during its passage down the ureter. Similarly an application of the Larssen diathermy electrode may set up waves of spasm in a retinal vein. Coats (1905) mentions the interesting possibility of "incomplete embolism." The plug stops at a part of the artery which it does not completely fill and the obstruction is made complete by spasm of the arterial wall.

(*c*) Was the white fundus background oedema? The rest of the retina was of tigroid type in Case 1. We cannot help thinking mere oedema less likely than the ischaemic necrosis of the ganglion cell and nerve fibre layers suggested by Coats (1913). Otherwise one would have expected to see more of the tigroid background than was shown after the vessels dilated. The same reasoning applies to Case 2. Oedema is obviously present in such cases as that described by Paton (1933). He saw Mr. H. E. Juler apply massage to an eye, when "the whole condition cleared up, just as if one had taken a sponge and had wiped the white oedema off the retina."

(*d*) Were any of the therapeutic measures taken of the slightest value to the patients in these two cases? We think the patient in Case 1 herself shifted the embolus by massage in the first instance. Mules (1888) reported a very similar case of an embolus shifted by massage of the globe. The amyl nitrite, acetylcholine, and mecholyl undoubtedly dilated contracted vessels, but the time-lag was too great for much benefit, except possibly in the case of the inframacular branch mentioned. The fact that the embolus was shifted along the lumen of the vessel made no difference—an absolute scotoma still corresponded with that particular area of retina. In Case 2 the patient claimed subjective improvement in vision after the vasodilator drugs, but no accurate estimate was

FIG. 5.

FIG. 8.

FIG. 11.

The section on the slide, shown in Figs. 11, 12 and 13, passes through the peripheral part of the disc, but not actually through the optic nerve itself. This small peripheral section of the disc shows some subacute swelling, with considerable patchy small-round-celled infiltration, some slight proliferation of fibro-blasts around the small and congested vessels supplying the disc itself, a slight degree of oedema, and—what is the matter of greatest importance—a section of *the blocked artery* itself, this being one of the larger branches of the central artery of the retina and this photograph is a very-low-power one, to show the general "geography" of the section. Below and to the left are nutrient vessels passing to the sclerotic and to a less extent through it to the choroid. These vessels, both small arteries and venules, as well as others in the neighbourhood not shown in the photograph, are normal in structural appearance and their walls do not show chronic thickening or any appreciable degree of inflammatory change, either acute, subacute or chronic. (The darkly stained structures are transverse and oblique sections of nerves, *not* vessels). (×30).

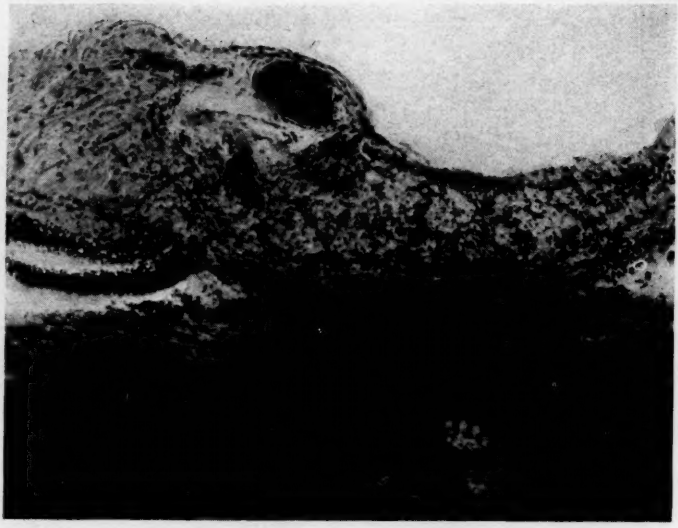

FIG. 12.

An ordinary low-power view of the peripheral portion of the disc, showing the blocked vessel, with its distinctly thickened walls and a small empty and contracted branch of the same vessel (its continuity can be traced in a neighbouring section) to the left, and a small empty vein immediately below these. Note also the moderate but distinct small-round-celled infiltration in the more central part of the disc and subjacent area of the cribriform part of the sclera, etc. (×100).

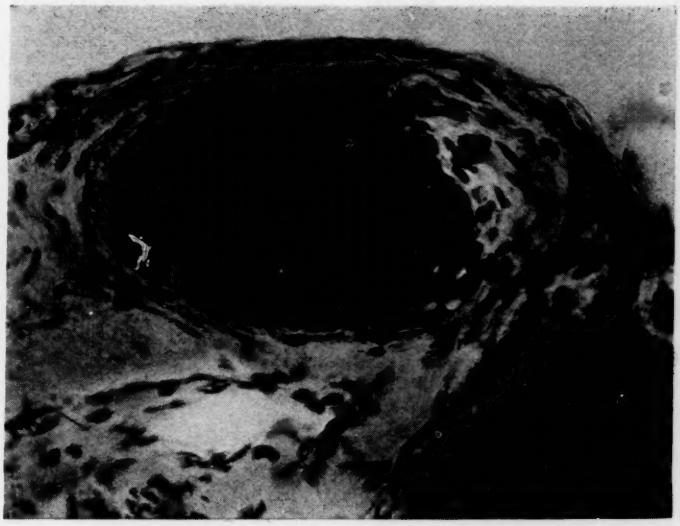

FIG. 13.

A high-power view of the blocked vessel and its immediate neighbourhood, the latter showing small-round-celled infiltration and an occasional polymorph below and to the right. The block in the lumen of the artery suggests an *embolus*, say a bit of impacted vegetation from heart-valve, rather than a portion of a thrombus formed *in situ*. Its looks " firm " and has definite edges. One can at a glance exclude the possibility of its being merely an agony-thrombus and still more so a post-mortem clot, as there is proliferation of the endothelial cells of the inner coat of the vessel, with actual buds of the proliferated cells " eating " into and absorbing little " bays " in its periphery (see also Figs. 14 and 15, to which much of this description also applies, and note the channel being " canalised " through it in Fig. 15). The proliferation at the right can be better studied in Fig. 14. (×400).

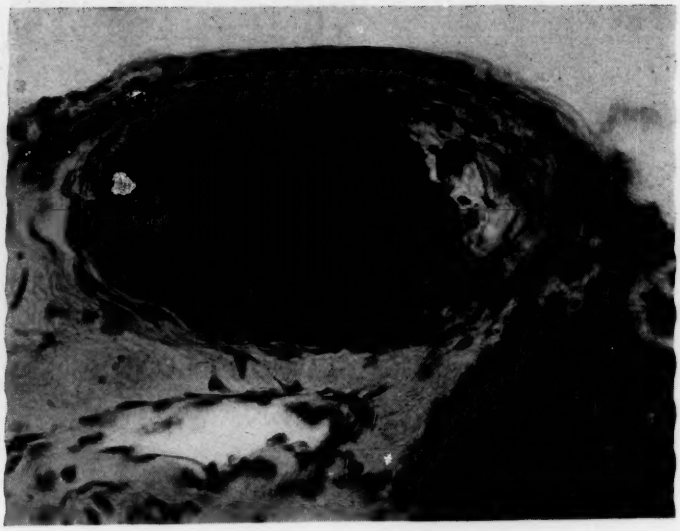

FIG. 13A.

This is from the same section as Fig. 13, but focused farther down into the thickness of the celloidin section, and so as to bring out the little buds of proliferating endothelial cells of the intima digesting their way into the "embolus," the edge of which looks firm and more "discrete" than in most of the ordinary thrombi formed *in situ*. Note the large bud of endothelial cells, the "shadows" of which can just be seen at the upper left-hand edge of the "embolus." (×400).

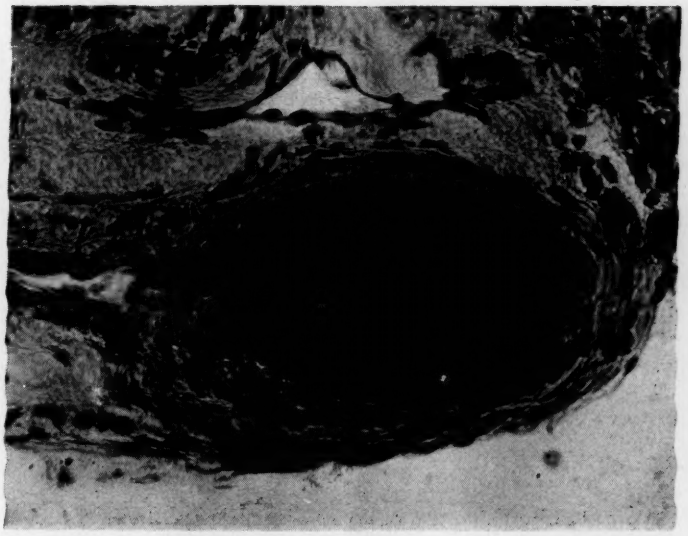

FIG. 14.

A neighbouring section through the body blocking the vessel. This shows the "firm" appearance of the mass with its well-defined edges, and the buds of proliferated endothelial cells of the intima digesting their way into its periphery. There are some non-haemolysed red corpuscles amongst the endothelial cells to the left, suggesting some degree of patency of the lumen, or perhaps some communication with the "canal" shown in Fig. 15. Note the contracted or semi-contracted left, which one would have expected to be thrombosed and blocked if the parent vessel had been merely "thrombosed." Note the small empty vein below. (×400).

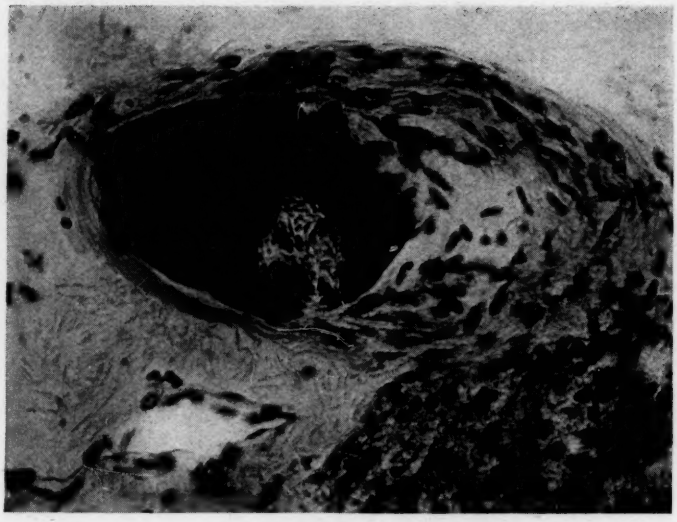

FIG. 15.

A further section through the embolus on its "far surface" (in relation to the appearances seen in Figs. 13 and 14). The celloidin sections are fairly thick, and, on focusing down into the deeper level, there is a suggestion of proliferated cells on its far surface, and from this far surface the "canalisation" well seen in this section has occurred. In this "canal" are closely-packed non-haemolysed erythrocytes and some leucocytes, as well as the canalising endothelial cells which show only as shadows round its periphery. To the right there is considerable proliferation of the intimal cells, suggesting that the process has been going on for a week or two. Note the "bud" attacking the periphery of the embolus immediately above the "canal." A portion (or tributary) of the small empty vein is seen below the artery. (×400).

FIG. 16.

A composite photograph of an area in which the pigmentary layer has remained attached to the choroid (which itself shows well-marked congestion and inflammatory cell-infiltration), and there is therefore no mechanically intermingled pigment-cell remains mixed with the debris on the deeper aspect of the retina. But, in this area of retina, there is definite and well-marked patchy subacute to slightly chronic granulation tissue thickening *on the inner aspect* of the retina, as well as irregularity of the ganglion-cell and thickening of the nerve fibre layer and internal limiting membrane. (×100)

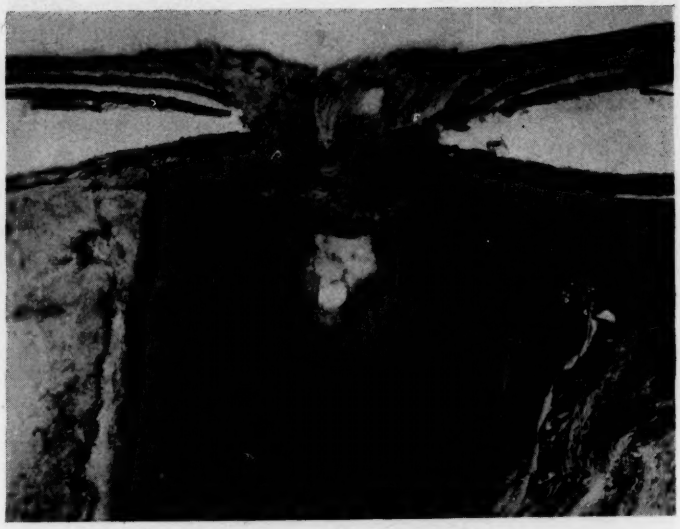

FIG. 17.

Section passing longitudinally through optic nerve and disc central to the position of the blocked artery seen in the previous sections illustrated in Figs. 11 to 15. There is a certain amount of chronic irritation in the region of the lamina cribrosa—but this is not a specially pronounced feature at this particular part of it: nor is there any great degree of this in the pial sheath of the nerve, nor of the arachnoidal sheath (though there is some little irregularity of its outlines), or of the dural sheath which forms the margin of the photograph on each side. The row of sections of small vessels on the right side are comparatively normal in appearance, only the third from below being filled with closely-packed red corpuscles, amongst which there is an excess of leucocytes. The white space in the centre of the nerve *just* touches the extreme periphery of the coats of a vessel, presumably the central artery, but in adjacent section no part of its lumen is available for examination. (×30).

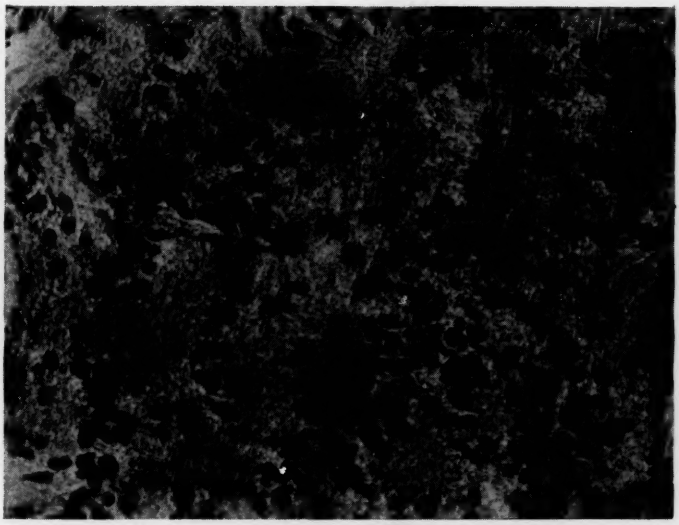

FIG. 18.

High-power view of a longitudinal section of the optic nerve near the nerve-head to show the subacute to chronic small-round-celled infiltration in the sheaths of the nerve-bundles. In various presumably normal optic nerves the amounts of fibrous tissue and of cells in the various parts of the sheath vary considerably in individual specimens, but the above photograph illustrates a distinct and undoubted excess of cells, though not of the fibrous tissues of the sheath itself. (×400)

FIG. 19.

A high-power view of a section of the choroid just to the left of the nerve-head (see Fig 11). It shows a small artery with thickened walls and almost empty lumen There is intense congestion and dilatation of the venules, one of these extending across the entire field, and another being seen below this to the right. Between the latter and the artery there is some subacute inflammatory cell-infiltration, also seen above the long venule, together with some extravasation of red corpuscles. The erythrocytes in the congested venules are discrete, with no obvious evidence of any thrombosis, and amongst the red corpuscles there were numerous collections of leucocytes, mostly polymorphs—not distinguishable in the photograph. There is, therefore, in this section, evidence of fairly chronic, subacute, and recent acute irritative phenomena in the eye. (×400).

possible. Orr and Young (1935) secured a therapeutic success with acetyl-choline. Emboli have been shifted with benefit in the cases of Mules (1888), Coverdale (1929), Butler (1927), Orr and Young (1935) and others so that in cases of retinal embolism vasodilator therapy seems worth trying in spite of its discomforts and even dangers (see Cushny, 1941).

2.—Pathological Considerations (W.E.C.D. and A.S.)

REVIEW OF LITERATURE

Few of the forty-odd cases of occlusion of the central artery of the retina examined histologically, are free from grave objections as to their validity for the elucidation of the nature of the occlusion or of the consequent changes in the retina. The classical case of von Graefe, who in 1859 introduced the concept of embolism of the central artery of the retina, was held by Leber —on histological evidence—to substantiate the view that occlusion of the central artery was embolic in origin but the broadened conceptions on vascular pathology that came towards the end of the last century led to the postulates that occlusion might also be due to changes in the arterial wall and to thrombosis; and Harms in 1905 could reasonably hold that the embolic nature of occlusion had not been proved anatomically in a single case.

Most of the eyes that have come to histological study are old in a double sense; the condition had been long-standing and the patient had been past middle age. In such cases, the changes observed in the artery are difficult to interpret. Is the organised obstructive mass in the vessel the primary lesion, with secondary changes in the vessel-wall; or are the changes in the vessel-wall primary, with secondary proliferative changes in the lumen? Furthermore old-standing retinal changes do not throw any clear light on the character of the immediate lesion in the retina in cases of occluded central artery.

The older literature has been fully reviewed by Coats (1906 and 1914), Harms (1905) and Leber (1915). The eclectic views of Harms who denied embolism altogether—or at any rate regarded it as unproven—represent an extreme but by no means untenable position. The studies of Coats and of Leber whilst upholding the significance of embolism, allowed for endarteritis and thrombosis as significant factors. No incontrovertible conclusions could be reached on the older material and it is only of late years that material less open to objection and examined histologically soon after the onset of the clinical symptoms has become available. This restricted material is also not always equivocal as can be seen from the following analysis:—

1. Velhagen (1905). Man, aged 40 years. Obstructed central artery with preservation of vision in area supplied by a cilio-retinal branch. Onset of eye trouble at the same time as aphasia. Endocarditis, mitral stenosis, moderate arteriosclerosis. Globe obtained post-mortem three months after onset of eye trouble and aphasia.

The histological findings in this case have been criticised by subsequent observers, especially Coats (1914). The obstruction is reported by Velhagen at the origin of the ophthalmic artery from the internal carotid artery. The site is unusual; an embolus at this site would probably be followed by the establishment of a collateral circulation; and the absence of any organisation in the clot is against expectation in a case of three months' standing. The presence of arteriosclerosis clinically—there was no general post-mortem examination—is a disturbing feature, even though it is reported that the retinal arteries showed "hardly any disease."

2. Früchte (1908). Man, aged 55 years. Established heart disease with a history of rheumatism. Loss of vision in the right eye with a characteristic picture of occlusion of central artery (cattle-truck appearance in the early stages). Infective endocarditis, with streptococci in the blood, followed by gangrene of right foot, infarcts in nose, spleen, kidney and liver as complications. Patient died 22 days after onset of eye trouble. Post-mortem examination showed old and recent endocarditis, aortic and mitral stenosis and insufficiency, and infarcts in various organs. Moderate arteriosclerosis was present.

Histologically, the central artery of the retina showed an almost complete obstruction immediately behind the lamina cribrosa. The arterial wall was normal, the endothelium being absent only where the embolus adhered to the wall. The obstruction was a homogeneous mass darkest at the centre and was surrounded by a layer of elongated cells. Staining for fibrin was negative. The ganglion-cell layer of the retina showed vacuoles and there was disorganisation of the rods and cones at the macula. The picture was complicated by congestion in the choroid with inflammatory cell reaction.

3. Rubert (1911). This is a case of great significance in the study of the early changes in the retina following occlusion, but has no validity in establishing the existence of embolism, for there is no evidence of any heart lesion and much evidence in favour of thrombosis as seen in marasmus.

A man, aged 41 years, underwent gastrostomy for stenosis of the oesophagus. Ten days later he developed blindness in the left eye with a classical picture of occluded central artery. Death from exhaustion ("weakness of heart, dyspnoea, etc.") four days later.

The changes in the central artery were somewhat similar to those described by Früchte. The retina showed marked oedema of the nerve-fibre layer with vacuolation and chromatolysis of the ganglion cells.

4. Meinhausen (1920). Man, aged 37 years, suffering from tabes and infective endocarditis. Three days before death he developed sudden blindness of the left eye with a typical picture of occlusion of the central artery, the obstruction being situated at the nerve head at the origin of the macular branches. Post-mortem there was found a patent foramen ovale, parietal thrombi in the right heart, and infarcts in the lungs and kidney.

Histologically the obstructing mass in the central artery was hyaline and fibrillated in structure, the fibres representing fibrin. The mass took on a brownish tint with v. Gieson's stain; nuclei and fragments of cells were present between the fibres.

The main retinal changes were oedema of the outer part of the internuclear layer, with large net-like vacuoles. The inner part of the internuclear layer was much less affected. The ganglion-cell layer was swollen particularly towards the macula, and its nuclei stained unevenly, some nuclei being darker than others; the cytoplasm itself was unchanged, but there was some vacuolation between the cells. The fovea itself was normal. The choroidal vessels were well-filled and contained an abundance of leucocytes. The walls of the retinal and choroidal vessels were normal.

5. Mohr and Böhn (1921). This is a case of bilateral occlusion of the central artery. A man aged 40 in 1918 had a war injury (grenade splinter) to his forehead

18 months previously, blinding him in both eyes for eight days. He returned to full service but was in indifferent health and in March, 1919, was diagnosed as suffering from heart and kidney disease. The left eye became suddenly blind six months later, followed by loss of vision of the right eye 14 days subsequently. There were the typical appearances of occluded central artery of the retina. Aortic insufficiency from endocarditis of the aortic valves was found. The patient became acutely ill with joint pains. A blood culture was negative and the Wassermann reaction doubtful. Within five weeks of the onset of blindness in the first eye the patient's condition warranted the diagnosis of embolus in the brain without focal symptoms. There was increasing cardiac failure; five weeks later the patient died suddenly after having developed erysipelas three days earlier. Post-mortem, aortic and mitral disease with vegetations were found, and there were infarcts in the spleen and localised thickenings of the walls of some of the cerebral vessels.

Histologically, both eyes showed obstructive masses behind the lamina cribrosa, interpreted as emboli. The retinal vessels here showed no endarteritis except in one peripheral branch, but it could not be asserted that they were completely normal. Especially massive changes in the retina were observed in the inner layers (nerve fibre, ganglion and inner nuclear layers). The maculae were affected and there was migration of pigment epithelium into the cone layer. The choroid showed hyaline degeneration of some vessels, with increase of leucocytes and the presence of streptococci.

6. Karbe (1924). A boy aged 12 years died of acute pulmonary tuberculosis, purulent bronchitis and broncho-pneumonia. About 36 hours before death the child had complained of loss of vision of the right eye, diagnosed as embolism of the central artery some 12 hours later.

Histologically the central artery in a horizontal section of the nerve showed the picture of a softening or pus-forming disintegration of a loosened thrombus in the stage of incipient shrinkage. There were no organisms. The artery itself was normal. There was mild oedema at the papilla in the ganglion cell layer. The nerve fibre layer was rather wavy but the nuclei of the ganglion cells stained well. There was no cellular infiltration in the oedematous area, and the rest of the retina was normal. The author believes the embolus to be derived from parietal-thrombus formations in the heart (which, however, was found normal and devoid of parietal thrombi at the post-mortem examination).

7. Engelbrecht (1924). A man aged 57, the subject of chronic suppurative ethmoiditis and sphenoiditis, developed occlusion of the central artery of the left eye. Four days later he underwent a radical operation on the sinuses under pantopon-scopolamine anaesthesia, but died three hours later without recovering consciousness. Post-mortem revealed nothing abnormal apart from the local sinus condition; the carotid arteries in particular were examined for thrombus-formation and the heart for any abnormality.

Histologically, the central artery was found normal in structure; there was no increase in elastic fibres. An obstruction incompletely filling the lumen was present in the region of the lamina cribrosa. It was an unorganised, partly a hyaline, partly a granular mass clearly separated from the intima of the arterial wall and was regarded as an embolus.

A sequel to this report is the note contained in an article by Scheerer (1925), who gives a personal communication from Engelbrecht changing the histological diagnosis of embolus to one of post-mortem clotting.

The cases of Schwitzer (1906), Shoemaker (1908), and Coats (1914), which are recorded as examples of embolus have no conclusive value, the first two because of the insufficiency of the data supplied, and Coats' case because of the complication by glaucoma and the advanced age of the patient (71 years).

That the picture of occlusion of the central artery can clearly be produced by lesions other than emboli is well illustrated by the case of Jaensch (1928) (and possibly also, that of Siegrist (1900)) in which it was due to extension of a thrombus from the internal carotid artery to the ophthalmic artery; and by the case of Velhagen (1915) in which the central artery was compressed by a haemorrhage into the optic nerve. It is of interest to note that both Jaensch's and Velhagen's patients had endocarditis, to which the lesion might uncritically have been ascribed.

The complexity of the problem is brought into still greater relief by the work of Scheerer (1925), who has shown that unorganised clots in both the central artery and vein at the lamina cribrosa are a common post-mortem finding. As already stated, Engelbrecht's final diagnosis of his histological findings in his case was that they were post-mortem artifacts. Scheerer, who re-examined the sections of Mohr and Böhm's case and those of Früchte's case, holds that these too show no organisation and represent post-mortem appearances. He is indeed critical of all the other recent cases since the eyes were removed post-mortem, and stresses that in Früchte's case clots of the same unorganised type as those seen in the central artery were present in the choroidal vessels.

One more factor in the causation of occlusion of the central artery (and vein) stressed by Scheerer (1923) deserves consideration. His studies of sclerosing processes in the lamina cribrosa have shown that this structure has pathological changes of its own, with secondary effects on the vessels; moreover the lamina may well have nutritive functions.

Of the seven cases in the newer literature, that of Engelbrecht can be dismissed as a clear case of post-mortem clotting. On the evidence of Scheerer, the cases of Früchte and of Mohr and Böhm must likewise be excluded. Rubert's case is distinctly less convincing than Früchte's and this applies still more to Karbe's case. Velhagen's case has been criticised by earlier writers so that the one case that can be regarded as valid is Meinhausen's. Unfortunately his description of the changes in the artery is scanty and does not contain any evidence indicating that the block of the artery showed signs of organisation.

The newer literature therefore does not add any undisputed cases of embolus to the older literature which brought forward much presumptive but no finally conclusive evidence.

3.—Histological Examination of the Eye in Case 2

The specimen (No. 42/22, Royal Eye Hospital Pathological Laboratory) consisted of the posterior segment of the right eye removed through the roof of the orbit 22 hours after death. It was hardened in formalin and fixed in celloidin. Serial sections were made and stained with haematoxylin and eosin. The conclusions of one of us (W.E.C.D.) were reached on histological evidence only.

The findings are illustrated in the photo-micrographs 11-19, and described in the legends. They may be summarised as follows:—

1. The choroid, retina, and optic nerve show considerable small round celled infiltration of the subacute to chronic type. This is

consistent with the septic process throughout the body induced by the subacute bacterial endocarditis. (Figs. 11, 12, 16-19).

2. The block in the artery (Figs. 11-15) is an embolus of some duration (probably several weeks) lodged in a vessel with a slight to moderate degree of previous thickening of its tunica media and adventitia, but not previously of its intimal coat. There are localised proliferative thickenings of the intima in the immediate neighbourhood of the embolus, which is just beginning to be canalized by endothelial buds which are invading its periphery. (Figs. 13-15).

3. The changes in the retina, proliferative and irritative, are not extensive and are most marked in the inner layers, though the rods and cones are also affected. These changes are largely subacute and probably date from the same time as the impaction of the embolus. There are, however, more recent acute changes, especially in the choroid, which shows an acute congestion of its venules which are distended with densely packed red blood corpuscles and a large number of polymorphs, indicating the presence of considerable leucocytosis just before death. (Figs. 16-19).

The histological evidence by itself is conclusive enough but taken together with the clinical and pathological evidence as a whole,—the heart lesion with vegetations, multiple embolic processes, the absence of any arteriosclerotic changes as also of thrombus formation—there can be no valid doubt as to the nature of the block.

Summary

1. Two cases of visible emboli in branches of the central artery of the retina with superadded spasm are recorded.

2. One of the patients died from subacute infective endocarditis 21 days after the onset of the ocular symptoms which themselves occurred six days before the full development of the symptoms of his fatal illness.

3. The eye examined histologically showed an embolus in the process of canalization.

4. On clinical grounds the occurrence of embolism as distinct from spasm, thrombosis and endarteritis of the retinal arteries can hardly be doubted. Clear histological evidence of this is, however, not available. The present study supplies this evidence.

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EXPERIMENTAL CORNEAL ULCERS*

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DURING recent years we have been working in Edinburgh on experimental ulcers and infections of the cornea of various types. This work started at the beginning of 1940 with the investigation of experimental mustard gas lesions on the eye and their treatment. In the course of this work it was found that secondary infection played an important part in determining the severity of the lesions produced by mustard gas; this not only affected the immediate reaction (corneal oedema and conjunctivitis) observed during the first week following contamination, but also the liability of contaminated eyes to develop delayed "vascularised keratitis" (secondary oedema with vascularization) starting about a week to ten days after the application of the gas. It was found that local treatment with chemotherapeutic agents decreased the severity of the primary reaction (which lasts for about a week following contamination), and also the liability of the eyes to develop delayed "vascularized keratitis" in rabbits. These experiments suggested that chemotherapeutic agents might be of value in the treatment of mustard gas lesions of the human eye and the treatment with sodium sulphacetamide (albucid soluble) is, to some extent, based on this work.

It became obvious, however, that much further work was necessary on the treatment of ocular infections, and it was of especial interest to determine how infections produced by different types of organisms could be influenced by treatment with chemotherapeutic agents and also with antiseptics.

There is much previous work on the production of experimental corneal infections with various organisms and this will be referred to later. In the case of B. pyocyaneus methods for the production of ocular lesions suitable for experimental investigation have been accurately described, but no such methods appear to be available for the study of infections produced by organisms like the pneumococcus, staphylococcus aureus and streptococcus haemolyticus, and suitable techniques had to be devised. As an extension of this work we have also studied experimental tuberculous lesions of the cornea. As will be seen such lesions have been previously described, but we have further studied them in

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order to obtain lesions suitable for the experimental investigation of the action of various therapeutic substances.

Value of such Experiments

It is worth while considering what information can be obtained from experiments of this type. In the first place, they may be of value in connection with injuries of the eye produced by toxic gases and other noxious substances, in so far as they are affected by secondary infection, and it is indeed with this end in view that this work was started originally; but, and possibly more important still, information can be obtained which is of value in the investigation of the aetiology and treatment of other lesions of the eye, and especially of different types of corneal ulcers. In connection with treatment, properly controlled experiments would allow us to obtain information on a variety of important points:

1. The relative value of various antiseptic and chemotherapeutic agents on lesions produced by different organisms.

2. The relative value of various methods of administration; in particular local and general (*i.e.*, systemic) methods of administration can be compared.

In this connection the suitability of various ointment bases for local application of substances can be studied. Furthermore various methods have been described for increasing the penetration of agents applied locally to the cornea, and it would be possible to study whether such methods do indeed increase the therapeutic results. For example, it has been suggested by Ridley (1940) that wetting agents should be used together with substances applied locally in order to increase their penetration. Iontophoresis is another method which has been suggested by Boyd (1943) to increase the penetration of sulphonamides.

3. Such investigations can be of value, not only in determining the effect of various treatments in eye conditions, but can give valuable information in estimating the effect of such substances in the treatment of infections with various organisms in sites other than the eye.

Human Corneal Ulcers.—A study of the literature shows that, in the human subject, many types of organisms can be concerned in the production of ulcers of the cornea, either of the simple or of the hypopyon type (see Weiss, 1943; Dickson, 1942; Duke-Elder, 1938.) With few exceptions, however, of which the pneumococcus is by far the most important, different organisms do not produce a characteristic clinical picture. The hypopyon type of ulcer is usually due to the pneumococcus, but to some extent the aetiological agent varies with the geographical location and with the occupation of the patient. Thus for example, in France the

diplobacillus of Morax (H. duplex) and of Petit are not infrequently concerned. In Palestine the Koch-Weeks bacillus (H. influenzae) has been recovered. In the Glasgow district the staphylococcus aureus was recovered in 25 per cent. of the ulcers examined, according to a study reported by Dickson (1942).

A variety of organisms have also been recovered in simple ulcers and it is of interest to note that in China marginal ulcers are frequently caused by haemolytic streptococci.

Experimental Investigations

(*a*) *Pyocyaneus ulcers.*—These are uncommon in man but the lesion is usually very severe when due to this organism. The experimental production of pyocyaneus ulcers in rabbits was first described by Axenfeld in 1908. In our own investigations we have produced equal lesions in both eyes of rabbits by removing equal areas of epithelium from both corneae and infecting these areas with a culture of B. pyocyaneus. For experiments on local therapy one eye in any animal can then be treated with the appropriate agent while the other untreated eye is used as control. That equal areas of epithelium have been removed can be confirmed by staining with fluorescein.

The lesions produced vary in severity in different animals, but are mostly equal in the two eyes of any one animal (in the absence of treatment.)

Twelve hours after inoculation the lesion has developed into an infected abrasion and 12 hours later definite corneal ulceration is present. Two to three days after inoculation the corneal ulceration is severe and fairly extensive and in some cases this may develop into a ring abscess with or without hypopyon. At the beginning of the second week the ulcer or abscess involves most of the cornea. Ultimately the lesion may (*a*) perforate and be followed by shrinking of the eye, or (*b*) develop into a grossly vascularised scar, usually with staphylomatous changes, or (*c*) occasionally the scarring may be limited to only about half the cornea.

Treatment.—Joy (1940) has shown that the course of such lesions in rabbits can be favourably influenced by the oral administration of sodium sulphapyridine. Shortly after this it was shown that the local application of a sulphonamide could also favourably influence the course of such lesions (Robson and Scott, 1941, 1942). When a 30 per cent. solution of sodium sulphacetamide was applied within 1 hour of inoculation ulceration was completely prevented in more than half the treated eyes, but when treatment was delayed for 12 hours its value was greatly reduced though there was still a definite effect.

Boyd (1943) found that iontophoresis increases the penetration of sodium sulphadiazine into the cornea and aqueous, as compared with simple diffusion. V. Sallmann (1942) investigated the value of this technique in the treatment of experimental pyocyaneus ulcers in the rabbit. He obtained the best results by a combination of sodium sulphadiazine iontophoresis and sodium sulphadiazine administration by the mouth and under these conditions beneficial effects could still be obtained when the treatment was started 24-30 hours after inoculation.

In contradistinction to these results, Klein and Sorsby (1943) found that sulphonamides did not control pyocyaneus ulcers. They probably used a strain of B. pyocyaneus which was resistant to sulphonamides. It is doubtful whether too much importance should be attached to such negative results, since it is easy enough to obtain negative results in chemotherapeutic experiments even when dealing with such a favourable organism as the haemolytic streptococcus.

Pneumococcal ulcers.—These are most important from the point of view of lesions in the human eye and therefore of great value in therapeutic experiments.

Ginsberg and Kaufmann (1913) described the production of infiltrates following the injection of a culture of pneumococcus into the cornea. They used these lesions in the investigation of treatment with various quinine derivatives and obtained some beneficial effects as judged by the action of these substances on the bacterial content of the infiltrates. Robson and Scott (1943 *a*) investigated the action of various strains of pneumococcus on the eyes of rabbits. Most strains injected into the cornea produce infiltrates but no ulceration; but the injection of a type 19 pneumococcus was followed by the development of ulcers associated with hypopyon and severe iritis with plastic exudation. The infection was obviously of a virulent character since about one third of the animals died from pneumococcal septicaemia, usually within the first 3 days following inoculation.

Method.—The young culture (6-15 hours) of the pneumococcus in plain broth is injected in both corneae of each rabbit to make small blebs. There is considerable variation in the severity of the lesion in different animals and especially in experiments performed on different days, but the lesions produced in both eyes of any one animal are usually very similar in character.

Twenty-four hours after inoculation there is slight infiltration at the site of inoculation and this is surrounded by a zone of oedema. The central part of the area stains with fluorescein and in the more severe cases there may already be the beginning of ulceration.

At 48 hours a definite ulcer is developed and this is surrounded

by a zone of oedema. There is subepithelial infiltration beyond the margin of the desquamated area and a fairly severe iritis can already be observed.

By the third day after inoculation a deep spreading ulcer about 4 mm. in diameter has developed and there is hypopyon and a severe plastic iritis. Subsequently the ulceration spreads both in depth and extent (see Fig. 1) and is accompanied by a massive

FIG. 1.

Microphotograph of pnemomococcal corneal ulcer on 14th day after inoculation (animal 1329); to show spread of ulcerative process under margin. (×35).

cellular infiltration of the substance of the cornea. The hypopyon at the same time increases in size.

During the second week there is a natural tendency to healing in these lesions and ultimately a dense vascularised scar is formed. Occasionally, however, the lesion is progressive and ultimately results in perforation of the cornea.

Treatment.—The local effect of a number of substances has been investigated. These were applied in solution at hourly intervals in order to maintain a high concentration in the cornea. The best results were obtained with penicillin, though quite striking effects were also seen with sodium sulphacetamide.

When the treatment with penicillin was started 1 hour after inoculation ulceration was completely prevented in 7 out of 8 eyes,

and only a small ulcer developed in the 8th animal. The control eyes all showed severe lesions. When treatment was delayed for longer periods the beneficial effect was greatly reduced, but some effect was still observed when the treatment was started 24 hours after inoculation.

The results with sodium sulphacetamide were not as good but quite marked effects were obtained when the treatment was started 1 hour after inoculation; when it was delayed for 12-24 hours the effects were slight.

A number of experiments were also performed with sodium sulphapyridine which appeared to be of some value in preventing the development of the lesion; unfortunately this solution is alkaline (pH > 10) and its repeated instillation in an inflamed eye produces quite marked irritation. It seems probable that alkaline solutions will not prove very suitable for local treatment of ocular infections since not only do they tend to produce an irritant action, but they also interfere with the natural lysozyme of the tears which produces its optimum antibacterial effect at the reaction of the body (Ridley, 1940).

There has been much discussion recently about the value of acridine derivatives, and especially of proflavine, in the prevention and treatment of sepsis (see Browning, 1943). A number of experiments were undertaken to determine whether proflavine would be of any value in ocular infections (Robson and A. A. B. Scott, unpublished data). It was found that, when treatment of pneumococcal lesion was started immediately after inoculation, a 0·1 per cent. solution of proflavine sulphate produced no beneficial effect whatever. With a 0·2 per cent. solution there was a slight beneficial effect, but this concentration of the drug produces irritation of the cornea and conjunctiva and would thus be unsuitable for clinical use. Proflavine was also tried in experimental staphylococcus aureus and haemolytic streptococcal infection (to be described below), but was found to be of comparatively little value.

Staphylococcus aureus lesions.—These organisms are uncommon in human corneal ulcers, though they were recovered from 25 per cent. of the ulcers (84 patients) investigated in Glasgow (Dickson, 1942). They are very common in lesions in rabbits due to irritant substances, *e.g.* in mustard gas lesions.

A number of attempts have been made to produce experimental lesions suitable for the investigation of therapeutic agents. Brown and Pugh (1936) succeeded in producing a fairly satisfactory ulcer in rabbits by the injection into the cornea of a strain of staphylococcus aureus found after many trials.

Robson and Scott (1943 *b*) tested a number of coagulase positive strains obtained from human lesions and chose the most virulent

of these for their further experiments. They found that the injection of an undiluted culture of this strain produced a very acute, almost fulminating, lesion unsuitable for therapeutic experiments, but found that by diluting it to a suspension containing 1500 organisms per c.c. satisfactory lesions could be produced.

Again equal blebs were produced by intracorneal injection into both eyes of rabbits, and although there were variations in different animals and especially in different groups of animals done at different times, the lesions which developed in both eyes of any one animal were amazingly similar.

In untreated eyes ulcers of varying severity developed and these were usually associated with hypopyon and iritis. In no case did the injection of the diluted culture fail to produce a corneal ulcer.

Twenty-four hours after inoculation the area stained with fluorescein and there was subepithelial infiltration at the margin.

At 48 hours the ulcer had already developed and a hypopyon was usually present. The lesion then increased in severity producing ulcers of various types and sizes. In some cases there was ultimately extensive necrosis of the cornea with or without perforation.

Treatment.—As was to be expected the local application of penicillin produced very striking results. The solutions available at that time were of low potency but even so they markedly inhibited the development of the lesion. The application of sodium sulphacetamide solutions, though less effective also gave definite results: 10 per cent. and 30 per cent. solutions appeared to be equally effective, but a decrease in the concentration of the sulphonamide to 2·5 per cent. made the treatment entirely ineffective.

Since sulphathiazole is amongst the most effective of the sulphonamides against staphylococcus aureus, this was applied as a powder to the experimental lesions, but was found to be ineffective. Sulphathiazole does not, however, readily penetrate into tissues and a soluble preparation, sulphathiazole sodium formaldehyde sulphoxylate was tried. This too proved to be ineffective.

The effectiveness of penicillin and of sodium sulphacetamide was greatly decreased when the interval between inoculation and the first treatment was lengthened and at 24 hours after inoculation neither of these chemotherapeutic substances was of any value. These results again emphasize the importance of early treatment.

In a number of experiments cultures were taken from the conjunctival sac in untreated eyes. Staphylococcus aureus could be recovered for a number of days after inoculation. Treatment with penicillin eliminated the organism from the conjunctival sac, but the application of sodium sulphacetamide did not have this effect. Hence the effect of an agent on the flora of the conjunctival sac

is not necessarily an absolute index of its effectiveness in the treatment of corneal lesions.

Haemolytic streptococcus.—This organism is uncommon in corneal lesions in the human subject though it is occasionally recovered. The experimental investigation of such lesions can, however, give valuable information about the effectiveness of various remedies in the treatment of infections with this organism.

Various investigators have produced experimental infections of the eye by the inoculation of the aqueous and vitreous (Rambo, 1938; Vence, 1939; Klein and Sorsby, 1943), but did not produce primary corneal ulcers.

Robson and A. A. B. Scott (1943, unpublished observations) injected a number of strains of haemolytic streptococcus into the cornea. In the majority of cases progressive lesions leading to ulceration were not produced. Two strains were, however, ultimately obtained which did produce corneal ulcers. One was recovered from the throat in a patient suffering from scarlet fever and this organism was particularly virulent and effective in the production of corneal ulcers; the other was recovered from an infected wound.

Method.—Undiluted cultures were injected into the cornea and produced lesions of the same type as those obtained with staphylococcus aureus, though a hypopyon did not form as frequently as with the latter organism. In order to make certain that the haemolytic streptococcus, and not some contaminant, was actually responsible for these lesions cultures were taken from the depth of the abscesses prior to ulceration. The infecting organism, *i.e.*, the haemolytic streptococcus, was in all cases recovered in pure culture.

Treatment.—A fairly concentrated solution of penicillin (220 units per c.c.) was available for these experiments and when the treatment was started 1 hour after inoculation the development of the lesion was practically completely inhibited. When the treatment was delayed for 12-24 hours the beneficial effect was only slight.

Unexpected results were obtained with sulphonamides (sulphanilamide and sodium sulphacetamide). They proved entirely ineffective when the treatment was delayed for 1 hour even though the strains tested proved not to be sulphonamide-resistant. When, however, the treatment was started immediately after inoculation quite appreciable beneficial effects were obtained both with sulphanilamide and sodium sulphacetamide.

Tuberculous lesions.—The production of experimental tuberculous lesions of the cornea was apparently first described by Langhans in 1867, *i.e.*, 15 years before Koch discovered the bacillus of

tuberculosis and established its causative relation to various forms of tuberculosis. The data of Langhans are not, at present, available and have been obtained from the paper by Haensell (1879). Both these investigators produced lesions in rabbits by injecting human tuberculous material into the cornea. After a latent period infiltration, vascularisation and caseation were produced. In some animals tuberculous lesions ultimately spread throughout the body (lungs, liver and other organs). Panas and Vassaux (1885) performed similar experiments and describe the growth of infiltrates by the formation of secondary tubercles around it, " mais, fait important, ce tubercule, arrivé au summun de son evolution, se reproduit, en émettant autour de lui de jeunes colonies qui ne tarderont pas à se rattacher à la source primitive, à s'ulcérer elles aussi, et concourir a l'agrandissement de l'ulceration ".

Igersheimer (1922) and Churgina (1930, 1931) produced tuberculous lesions of the cornea by the injection of cultures of the organism. They also investigated the effect of one localised tuberculous lesion against a second inoculation of the organism and found that some protection was given.

We have investigated the production of tuberculous lesions of the eye suitable for the study of the action of chemotherapeutic substances (Robson and A. A. B. Scott, unpublished observations). For this purpose it is important that equal lesions should be produced in both eyes of any one animal and that the minimum inoculum which will produce a suitable lesion in all animals be used. This will of course give the optimum conditions for the action of chemotherapeutic agents.

We have used two strains, namely :

(*a*) bovine strain from the National Type Collection.

(*b*) human strain isolated from a tuberculous lesion of the human eye.

Suspensions of the organisms were injected into the cornea and in every experiment in which 100 or more organisms were injected tuberculous lesions have been produced. The actual amount of fluid injected into the cornea is about 0·01 c.c. and the minimum amount of bovine culture with which a lesion has been produced is 0·00001 ug. This contains about 5 organisms.

The course of the lesion with the bovine and human strains was rather different.

Lesion with bovine strain.—This produces a lesion of the ulcerative, caseative type. After a latent period of a week or more, depending on the dose inoculated and during which period only the lesion produced by the needle track is seen, macroscopic infiltration begins to develop at the site of inoculation. This sometimes seems to be made up of a number of small nodules. The

infiltrate gradually increases in size and minute nodules appear around it. Vascularisation starts at about two weeks or more after inoculation. The minute outlying nodules increase in size and coalesce with the growing main infiltrate.

At about three weeks after inoculation the infiltrate breaks down producing caseating ulceration. Simultaneously vascularisation spreads from the periphery towards the centre but the central caseating area which can be of considerable size in the more severe cases, does not become vascularised. Nodules are continually forming under the vascularised area and may spread into the conjunctiva and sclera. Occasionally the central ulcer may perforate.

General dissemination of the tuberculous process may occur, secondaries being found in the cervical lymph glands, lungs, kidneys, etc.

Lesion with human strain.—This produces a more benign type of lesion with a typical macroscopic appearance. There is less tendency to caseation and ulceration and in the great majority of cases the lesions tend to regress after three or more months. We do not know of course whether the differences between these two strains will apply to all bovine and human strains or whether they are merely due to differences in their virulence.

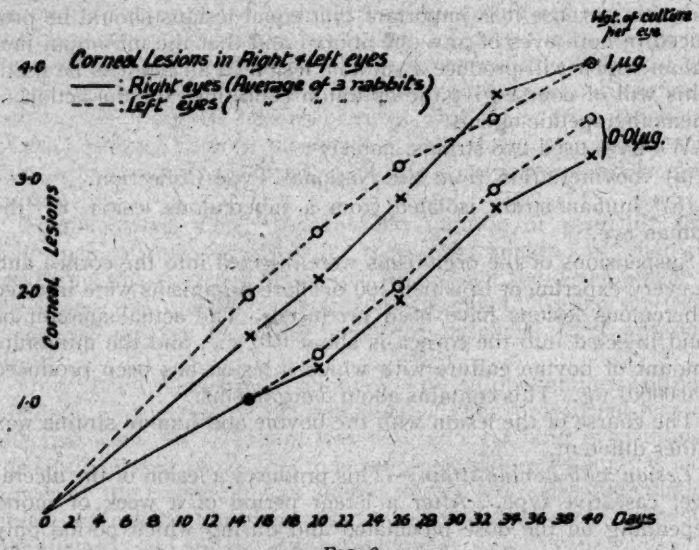
Wgt. of culture per eye
Corneal Lesions in Right + left eyes
——: Right eyes (Average of 3 rabbits)
– – –: Left eyes (" " ")
1 µg.
0·01µg.
Corneal Lesions
4·0
3·0
2·0
1·0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 Days

FIG. 2.

Showing the development of tuberculous lesions in the right and left eyes of groups of rabbits.

We have studied quantitatively the development of the lesions of both eyes of a number of animals and found that they progress at a remarkably equal rate. This is illustrated in Fig. 2.

The investigation of the treatment of these lesions is still at a very early stage. So far only lesions produced by massive injections have been treated, and the results have been negative, but further investigations are in progress.

The experiments performed in Edinburgh and referred to in this paper were carried out in collaboration with Colonel G. I. Scott and Major A. A. B. Scott. We are greatly indebted to the "W. H. Ross Foundation (Scotland) for the Prevention of Blindness" for their financial support and to Dr. Sinclair and Colonel Dickson for their interest. We are grateful to Dr. Levinthal, of the Royal College of Physicians Laboratory, Edinburgh and to Dr. Oag, of the Department of Bacteriology, University, Edinburgh, for valuable bacteriological help.

Dr. Trevan, of the Wellcome Research Foundation, kindly supplied us with Penicillin and sulphathiazole sodium formaldehyde sulphoxylate, and Mr. Edwards of British Schering, Ltd., with sodium sulphacetamide (Albucid soluble).

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A STUDY OF EPITHELIAL REGENERATION IN THE LIVING EYE

BY

IDA MANN

OXFORD

THERE is general agreement that epithelium heals by migration and multiplication of epithelial cells (Arey, 1936). Migration from the edge of the denuded area occurs first and is followed later by mitosis at some distance from the defect so that the loss is made good by pre-existent cells which move actively across to cover the raw zone, these cells themselves being replaced by cell division behind their orginal positions and not over the wound area. Both events have been demonstrated by observers on microscopic preparations of dead tissue, but it is our object to call attention to an experimental and (in suitable cases) clinical method whereby the process can be watched in action in the living eye.

The first observations similar to these* were made by Leber (1891), who appears to have been uncertain about the cause of the migration for he was not always able to convince himself of the previous existence of a defect in the epithelium, though he suspected it and in every case a minute defect must have been present as the experiments involved injections into the anterior chamber. An account of Leber's experiments was given by von Hippel in 1928 in which he discussed the phenomenon of epithelial migration in relation to inflammation. Ranvier also (1898) dealt with the subject in his work on healing of corneal and conjunctival wounds. He pointed out that in clean wounds of the corneal epithelium only the healing occurs by sliding from both edges of the wound and is complete in 24 hours. Neither plastic lymph, fibrin nor mitoses are required in the healing of small wounds of the cornea. He states that the process does not appear to hold good for conjunctival wounds in which a reaction of the underlying cells is also involved. It would appear probable from the experiments about to be described that if the conjunctival epithelium alone is removed and the sub-epithelial tissue not injured the process of healing by sliding is the same as in the cornea. Werner (1902) and Marchand (1924) have also described the sliding process. H. W. Florey and H. E. Harding have observed the same phenomenon in experimental ulcers of the duodenum.

The most convincing microscopic demonstration of the process has been given by V. B. Wigglesworth in his paper on " Wound

* The process was first observed in 1941 when studying the effects of mustard gas.

Healing in an Insect" from which Fig. 1 has been taken. He used a blood-sucking bug (Rhodnius prolixus hemiptera) in which, once growth is complete, no further mitoses occur in the simple layered epithelium. His preparations show the stages of activation of the cells along the edges of the wound, followed by migration to the site of injury over which they spread. This leads to a thinning of the cells in the zone further out where mitoses then occur to bring the number of cells back to normal. Fig. 1 shows the covering of the defect by thinning and sliding and also the

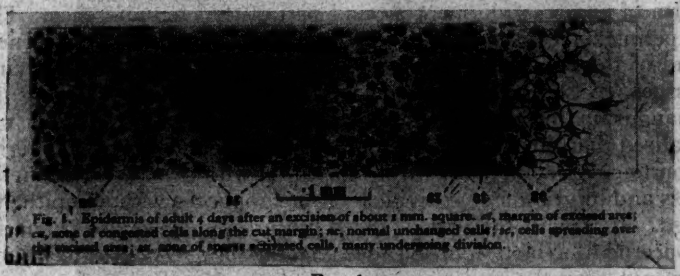

FIG. 1.

Reproduced by kind permission of Professor Wigglesworth from the Journal of Experimental Biology, 1937, Vol. XIV., p. 368. This plate shows the arrangement of cells in the healing insect epidermis. Epidermis of adult 4 days after an excision of about 1 mm. square. *ct*, margin of excised area; *cs*, zone of congested cells along the cut margin; *nc*, normal unchanged cells; *sc*, cells spreading over the excised area; *ss*, zone of sparse activated cells, many undergoing division.

zone of mitoses. He states that in this animal the migration begins in 6 hours and is usually complete in 2-3 days. The mitoses in the adjacent zone increase to a peak in 6-7 days. He considers that the substance which activates the sliding cells is a product of the autolysis of the injured cells and is neither tissue nor species specific. It is destroyed by heat so that the healing of a burn may be accompanied by mitoses at the spreading edge itself and not a migration.

The experiments which we are about to describe are applicable to any species which shows pigment in the basal cells of the conjunctival or corneal epithelium, since the presence of the pigment allows one to recognise the particular cells involved and to follow their migration from day to day, in response to various types and sites of injury. The movement of the pigment can be seen in many cases with the naked eye and in all cases with a corneal loupe. Slit-lamp examinations were also made, but are not necessary for the observation of the phenomenon. The presence of the

initial loss of epithelium was assured by the use of fluorescein and in no case was a slide observed apart from an epithelial defect. The observations were made on rabbits and were confirmed clinically in man on Africans.

Experiments.—A series of 120 eyes of 82 rabbits of crossed Dutch strain (black and white) with some pure black and some wild colour with brown eyes were used. These rabbits were all suitable because they had pigment in the basal cells of the limbal epithelium, either in the form of a complete brown ring around the limbus, about a millimetre wide and easily visible, or in the form of an arc of pigment around part of the circumference. The experiments consisted of injury to the epithelium of the cornea, and of the conjunctiva with and without injury to the underlying tissues, by scraping, by chemicals and by heat. In studying the changes in the position and shape of the pigment ring it was realised that three processes might affect it, namely, simple migration to cover epithelial loss, proliferation with or without epithelial loss and migration of individual chromatophores without epithelial loss. It is with the first of these processes that we are primarily concerned. Ninety-four eyes were studied for responses to injury. Twenty eyes showing pigment proliferation as distinct from migration were studied and will be briefly described for contrast with the first group, and to make the picture of migration in response to injury complete, six eyes were observed in which migration without injury had been induced by dietary deficiency. These three types are quite distinct and can be readily distinguished so that in the series of 94 eyes there is no doubt that the movement of the pigment ring occurred as a result of the loss of epithelium.

The first series of experiments is designed to demonstrate the movement in its simplest form in response to simple superficial injury. If a rabbit's cornea is abraded with a Tuke's knife or other suitable instrument over a narrow area 2·5 mm. from the pigment at the limbus and parallel with it, taking care not to injure the underlying substantia propria, the pigment ring adjacent to the injury will show an irregularity, apparent in less than 20 hours. This (Fig. 2A and B) irregularity affects the inner but not the outer edge of the pigment band and gradually increases until an even fringe has almost reached the denuded area. It does not pass across this, as it meets the slide from the opposite side which in the absence of pigment cannot be seen in life, but can be inferred from the position of the pigment and from the loss of staining with fluorescein. The margins of the slide on both sides show with the slit-lamp a faint epithelial bedewing which disappears when the two edges have met. The pigment in the slide remains stationary and visible macroscopically (Fig. 2*a*) for some time, and

very gradually becomes sparser, scattered grains remaining visible for many months, but being finally lost as the cells containing them are eventually shed. The original limbal pigment ring persists, though it may show a sparse area for some time.

If, after such a pigment fringe has been produced and has healed, the cornea is further injured by scraping off the epithelium

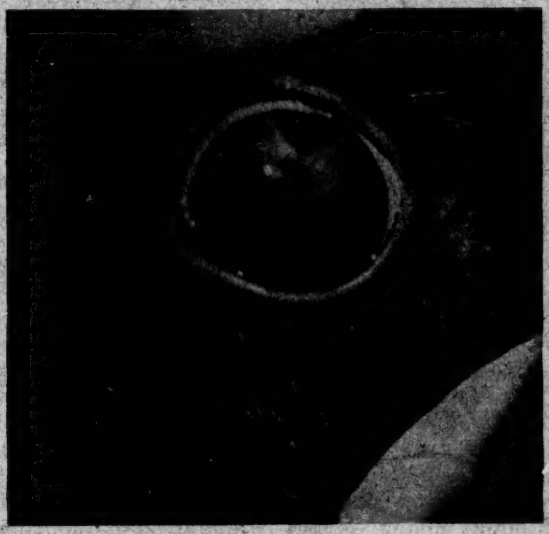

FIG. 2A.

FIG. 2B

(*a*) Photograph of rabbit's eye with triangular pigment slide above, easily visible macroscopically.
(*b*) The upper limbus of a rabbit's cornea. The shaded portion shows the area over which the epithelium had been scraped off the previous day. It was 2·5 mm. from the limbus. The pigment ring (dotted area) is sliding towards it as a fringe.

as before, but over a similar area 2·5 mm. nearer to the centre of the cornea, a further slide can be produced, the original pigment fringe crossing over the site of the original injury and approaching, but not necessarily reaching, the centre of the

new injury (Fig. 3). In this way a slide can be made to approach the centre of the cornea in successive stages, but if the initial injury is made 5 mm. from the limbus, then no movement of the

FIG. 3.

The upper limbus (seen in Fig. 2*a*) after a further injury (abrasion) 2·5 mm. from the first and therefore 5 mm. from the limbus. The pigment has now crossed the site of the first injury and is approaching the second. Eight days from the second and 11 days from the first.

FIG. 4.

A pigment slide towards a portion (central) of a burn of the cornea 2·5 mm. from the limbus. Two days after injury. Sliding has occurred at 2 only.

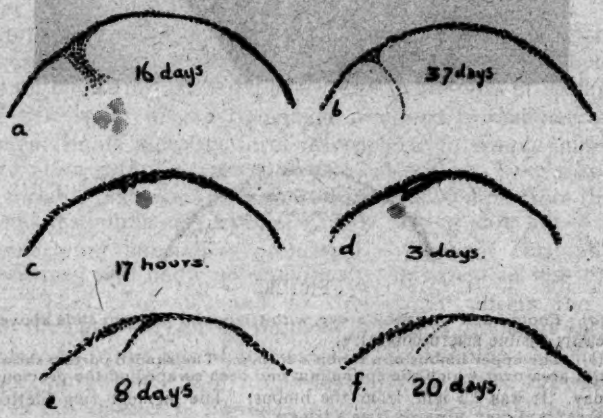

FIG. 5. Diagrams showing a tongue-like slide.

(*a*) A narrow fringe running towards a small lesion, the previous position of which is shown as three shaded spots. Sixteen days.
(*b*) The same slide at 37 days.
(*c*, *d*, *e*, *f*) Four successive stages in the formation of a linear slide in response to a small round abrasion 2·5 mm. from the limbus.

pigment ring will take place. In this case there is sufficient unpigmented epithelium between the wound and the limbus to cover the denuded area. This gives us some idea of the area of spread of the activating substance from a simple removal of epithelium. It seems to be more than 2·5 and less than 5 mm. from the edges of the wound in all directions. If instead of removing the epithelium by scraping, the cornea is burned with a hot wire then the amount of sliding produced is very much less, the movement of the pigment being very irregular and not occurring all along the burned area. It is probable that migration occurs only towards the less severe parts of the burn if Wigglesworth's contention that heat destroys the activation is correct. Fig. 4 shows three small burns, the first and third being made with a hotter wire than the second, towards which alone migration has occurred, though all three have healed, the first and third presumably by mitotic division from their edges.

If instead of abrading an area parallel with the limbus a small round lesion is made (at 2·5 mm. from the edge of the pigment) then instead of a fringe, a linear slide will be produced. At 24 hours there will be a slight irregularity and at three days a narrow tongue of pigment will detach itself and approach the wound, becoming longer and thinner as this heals (Fig. 5). If the conjuntival epithelium is removed without injury to sub-conjunctival tissues then a reversed slide will be produced by the corneal epithelium migrating outwards to make up the loss, (Fig. 6). Sometimes only fringing occurs, sometimes the whole limbal band migrates, as in Fig. 6, in which the destruction of the conjunctival epithelium was produced by a minute application of mustard gas and not by scraping.

If the pigment ring itself is scraped off there is very little tendency for regeneration by migration of the two ends towards each other. The sliding appears to occur at an angle to the limbus and not along it. The abrasion heals in three days or less, but pigment does not appear in any quantity in the gap until the eighth day, when scattered grains are visible which only very slowly in the course of months spread in the damaged area, and never completely reconstitute it.

The second series of experiments deals with the form of slide produced by damage to larger areas of the cornea. In these experiments the epithelium was destroyed by the use of chemicals. In some cases the epithelium alone was damaged and in others the corneal corpuscles in the underlying area were killed to varying depths. In all cases, however, the behaviour of the limbal pigment ring was determined by the area of destruction of the corneal epithelium and not by the condition of the substantia propria nor

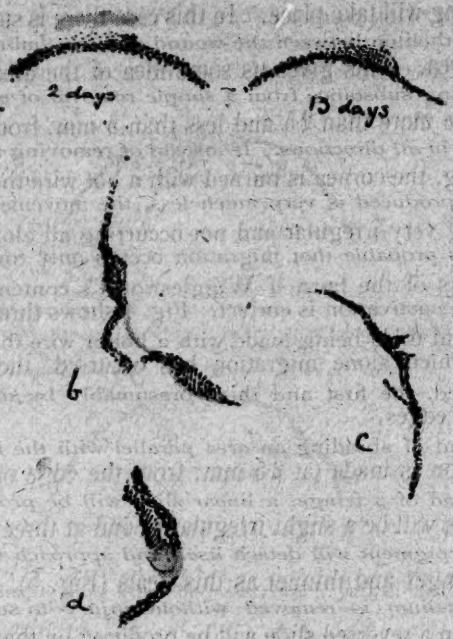

FIG. 6.

(*a*) Two stages in a reversed pigment fringe produced by an abrasion of the conjunctival epithelium. The shaded portion shows the position of the lesion.

(*b*) A slide of the whole width of the pigment ring on to the conjunctiva following an injury with mustard gas.

(*c*) Fringes on to cornea and conjunctiva from very small lesions on either side of the limbus.

(*d*) A pigment fringe on the 3rd lid of a rabbit produced by a lesion with mustard gas in the shaded area.

by the nature of the chemical used. Even in cases in which the corneal corpsucles were destroyed and the substantia propria rendered oedematous, the process of healing occurred by migration in the same way and during the same period as when the injury was a simple abrasion. This also held good when the injury was sufficient to produce vascularisation which proceeded subepithelially after healing. Although changes in the epithelium covering such an injured substantia propria might occur later (secondary oedema or complete breakdown) in most cases healing of the superficial loss was complete (as evidenced by disappearance of staining with fluorescine) in four days, while the pathological process continued its course deep to the epithelium for days or sometimes weeks

afterwards. This finding is in agreement with the recognised conception of the epithelium being as it were parasitic on the substantia propria; it is probable that it receives some at least of its nutriment from its superficial surface, *i.e.*, via the lid and lacrimal secretions and is not dependent on the state of the underlying substantia propria for its existence (Pirie).

The chemicals used to destroy the epithelium included some, such as acetone, which destroy the epithelium alone, and others, for example formalin, which penetrate and temporarily alter the whole thickness of the cornea. Hydrochloric acid, chloroform, ammonia and mustard gas all produced similar results on the epithelium, though they differed from each other in their deeper action. A variety of chemical warfare agents was tried, but the chemical used appeared to be immaterial so long as the localised epithelial injury resulted. The types of migration would seem to fall into categories based on shape and to be determined by the

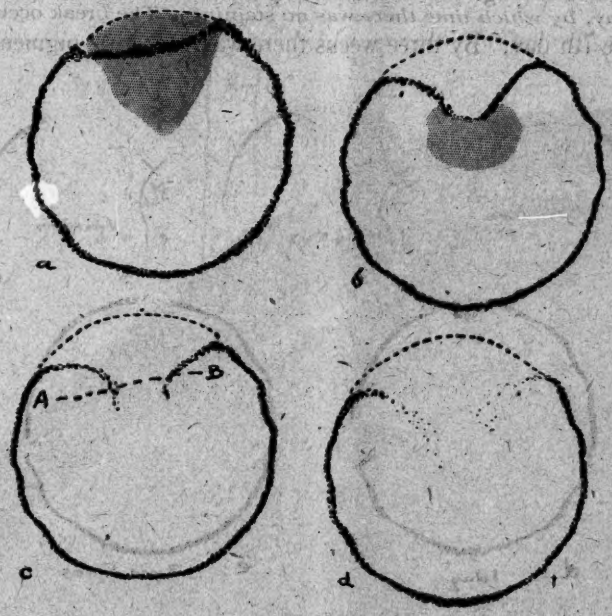

FIG. 7.

Four stages in the healing of a large sectorial lesion (shown shaded in *a*). The limbal pigment ring slips inwards without a break until the staining has gone at four days. The break occurs (*b* & *c*) at six to seven days and by 14 days (*d*) the pigment is sparse and widely scattered. The gap in the ring at the limbus is permanent. The line A B in (*c*) is the line of section in Fig. 9.

size and site of the initial denuded area as shown by fluorescein staining.

The movement of the pigment-containing cells starts at or before 18 hours. It is most obvious on the 3rd or 4th day (average from 93 cases) and reaches its maximum always within a week. After this the pigment grains begin to thin out and appear sparser, gradually disappearing. In some cases of small slides no trace is left after 10 days, but in many cases traces persist for 3 weeks and in some for as long as 4 months. In practically every case the defect was covered (as evidenced by cessation of staining with fluorescein) in 4 days.

We can consider first the effect of a sectorial lesion (Fig. 7) which produces a displacement inwards of the whole segment of the limbal pigment ring. This may break in its centre and the two ends curve in towards the centre of the cornea. The pigment grains become sparser and gradually disappear. In the rabbit illustrated in Fig. 7 the inward displacement was marked on the 4th day, by which time there was no staining. The break occurred on the 7th day. By three weeks there was very little pigment left

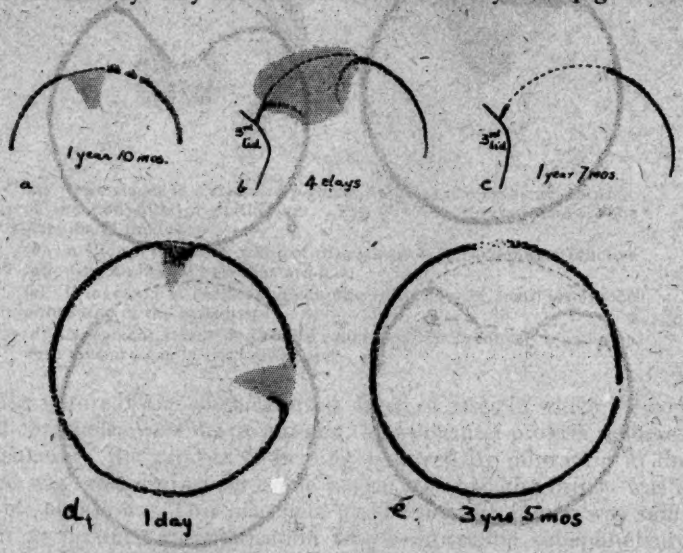

FIG. 8.

Three cases of break in the limbal ring without regeneration, (*a*) 1 year 10 months after chemical injury in shaded area, (*b* & *c*) two stages of a limbal lesion (four days and 1 year 7 months), (*d* & *e*) two stages of two minimal limbal lesions in the same eye (1 day and 3 years 5 months) showing that only very slight regeneration occurs even in small breaks.

and in a month it had disappeared. The gap in the limbal pigment never completely regenerates when the whole width of the ring has migrated. Irregularities, thin areas and actual gaps persist and have been observed for 3½ years, even after relatively small breaks. The pigment which is displaced, however, disappears entirely and there is no attempt at persistence in the new position (Fig. 8). When fringing only has occurred, as pointed out in the first series of experiments, the migrated pigment disappears, but the ring from which it came persists though it is often a little sparser opposite the slide for some time. The permanent disappearance of the pigment after a complete slide is curious, since if the basal cells have taken part one would expect them to continue to produce pigment in their new situation and if they have not, one would expect the ring to regenerate from them in the original position. Fig. 9 appears to show migration of the whole thickness of the epithelium including the basal cells. It represents a section through a pigment slide.

FIG. 9.

Microphotograph ×100 of the corneal epithelium in the pigment slide see in Fig. 7c, showing the pigment and a polymorphonuclear reaction in the underlying substantia propria.
(*a* & *b*) Pigment in the epithelial cells.
(*c*) Mucus cells derived from the conjunctiva by sliding.

If the lesion is not quite so extensive then the actual break may not occur, the pigment line being merely displaced on to the cornea and gradually fading away, *i.e.*, disappearing from stage 1 of Fig. 7.

If the lesion is very extensive the most widespread and bizarre slides may be produced. Fig. 10 shows the maximal slide produced. The epithelium of practically the whole cornea except the

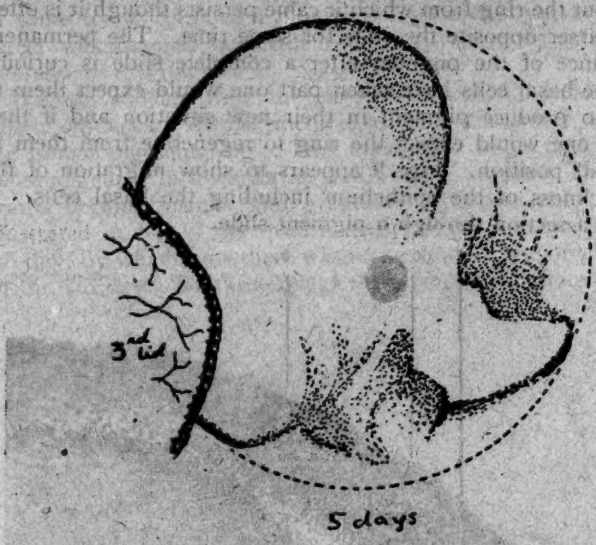

FIG. 10.

A very extensive pigment slide five days after almost complete destruction of the corneal epithelium.

limbus had been destroyed. Fig. 11 shows two other large pigment slides of varying pattern.

These experiments emphasize this method of corneal healing and show how the relatively large areas of destruction are made good in so short a time. This is in line with the common clinical experience of the rapid healing of corneal abrasions in man, but owing to the absence of any landmark it is impossible to be sure that the process is one of migration and not of cell division. If, however, the eyes of Nigerians, who possess a pigment ring even wider and more striking than that of a rabbit, are examined after small injuries such as the removal of a corneal foreign body, a similar demonstration of sliding can be seen. Fig. 12 shows two pigment slides (a fringe and a linear migration) from

the eyes of two Nigerians. One (*a*) only vaguely remembered the injury so that it must have been some time before, the other (*b*) complained that a spark or small foreign body in a blacksmith's shop had gone into his eye a few days before.

FIG. 11.

Two large pigment slides.

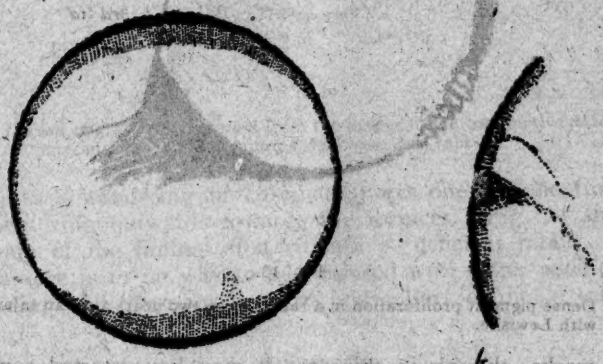

FIG. 12.

The eyes of two Nigerians after corneal foreign bodies. In Nigerians the pigment is present on the cornea itself as well as the limbus proper. It forms a ring wider above and below, encircling the cornea.

The third series of experiments deals with the production of pigment proliferation in response to chemical injury and its differentiation from simple migration. The simplest way of producing pigment proliferation in the rabbit appears to be by injuring the eye with any of the arsenical war gasses. The injury should be

severe enough to produce a dense vascularising keratitis, but not sufficient to cause perforation and collapse of the globe. The matter is only of interest here in showing the distinction between such increase and misplacement of pigment and that due to the epithelial migration described above. The pigment proliferation did not occur until after the healing of the epithelium, so that it was never apparent within the first 4 days, as the pigment slide always was. The prolifieration was produced in 20 eyes, the earliest time being 30 days after the original injury and the longest

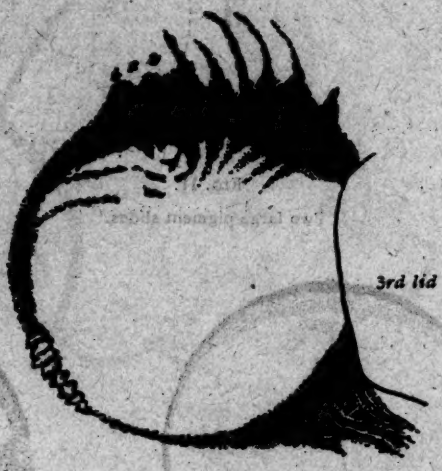

FIG. 13.

Dense pigment proliferation in a rabbit's eye two years after an injury with Lewisite.

nine weeks, though in this case it may have started somewhat earlier. The overgrowth of pigment was progressive and continued to increase for months (in one case for two years). The appearance was distinctive, the pigment being in dense masses arising from the limbus and spreading both on to the cornea and on to the conjunctiva (Fig. 13). There had not necessarily been an original pigment slide. The figure shows the very distinctive appearance which is not likely to be mistaken for a simple epithelial slide.

The fourth series of experiments exemplifies an already known phenomenon of pigment migration from the pigment ring on to

the conjunctiva in cases of vitamin A deficiency. This migration gives rise in man to the diagnostic smoky conjunctiva of A deficiency in pigmented races. It can be produced experimentally in rabbits and serves as an example of pigment migration without epithelial loss. It is not in the nature of a generalised slide, but

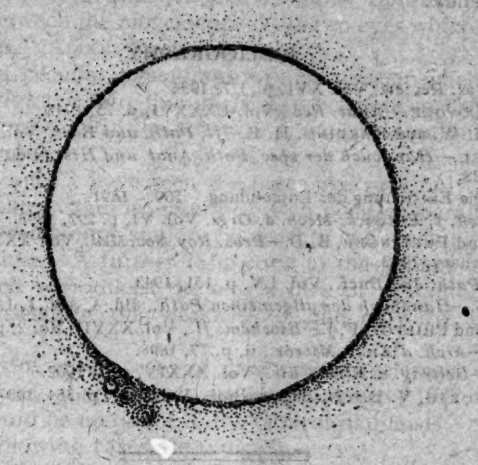

FIG. 14.

Diffuse migration of pigment from the limbus to the conjunctiva without antecedent injury in vitamin A deficiency in a rabbit.

suggests a wandering of chromatophores one by one from the pigment ring outwards towards th fornices. Fig. 14 shows a diagram of the limbus of a vitamin A deficient rabbit. The appearance is in no way to be confused with either proliferation or sliding and there has been no preliminary epithelial loss.

Summary

1. The sliding or migration of healing epithelium has been demonstrated in the living eyes of rabbits possessing a pigment ring in the conjunctiva at the limbus, and also in Nigerians who show the same condition.

2. The slide can be produced by simple trauma or by chemical injury. It is not so easily produced by heat.

3. The shape of the slide is determined by the shape and position of the epithelial loss and can occur on to the conjunctiva or the cornea equally.

4. The rate and shape of the slide do not appear to be influenced by the nature of the injury nor the condition of the underlying substantia propria.

5. The sliding of a pigmented limbus after trauma can be distinguished from pigment proliferation after chemical stimuli and from pigment migration without epithelial loss in vitamin A deficiency.

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ATAXIC NYSTAGMUS: A PATHOGNOMONIC SIGN IN DISSEMINATED SCLEROSIS

BY

WILFRED HARRIS

LONDON

FOR many years I have observed this peculiar form of nystagmus, and have demonstrated it to numbers of students and to my clinical assistants as being diagnostic of disseminated sclerosis. In my experience it is not met with in any other condition. On June 28, 1943, I showed a case illustrating this condition at the clinical meeting of the Medical Society of London, held in the wards of St. Mary's Hospital. As this aroused a certain amount of interest, and no-one who saw the case appeared to have observed this form of nystagmus previously, I feel that a description of its peculiarity should be put on record.

When the eyes are turned laterally, the conjugate action appears weak, so that the inner eye, *e.g.*, the right eye when looking

towards the left, does not reach the inner canthus, but the outer eye shows coarse nystagmus, the eye reaching the outer canthus with a quick movement, and a slower return, as though the outward movement could not be maintained, owing to weakness. Usually this nystagmus of the outer eye continues as long as the patient looks in that direction, the inner eye meanwhile remaining stationary, not having quite reached the inner canthus. It is this discrepancy between the movements of the two eyes which suggests to me the term " Ataxic Nystagmus."

Usually this peculiar nystagmus will be present when looking either to the right or left, though it may be more marked in one lateral movement than in the other, or it may be seen only in one lateral direction.

In one case only I have seen the outer eye give only one flick as far as the outer canthus, returning to a position parallel to the inner eye and remaining stationary, neither eye reaching quite to the outer canthus. A further injunction to the patient to look to the right or left reproduced the single flick of nystagmus of the outer eye, illustrating the weakness of the outward conjugate movement.

I have notes of seven cases of disseminated sclerosis with this type of nystagmus that I have seen since January, 1942, in all of which there could be no doubt of the clinical diagnosis.

The three following cases are typical :—

Mrs. *C.*, aged 44 years, seen June 4, 1942. Two years weakness in walking and standing, unsteady on her feet, and cannot walk alone. Precipitancy of bladder. Somewhat anaemic, but blood film normal. K. J. + +, Plantars extensor, vibration sense in legs lost. Well marked ataxic nystagmus in both lateral directions. W. R. negative in blood and C. S. F. 4 lymphocytes per c. mm. Lange 2222111000. Protein content normal. She was shown at the Medical Society of London meeting on June 28, 1943.

P. F., a man, aged 50 years, seen October 2, 1942. Unsteady gait for nine years, getting gradually worse, can now only drag himself about by holding on to furniture. Legs spastic, plantars extensor, pallor of discs. Slow ataxic nystagmus in both lateral directions. For the past twelve months spasmodic neuralgia in right upper and lower jaws, especially in tongue, brought on by eating and handling the face. Had several injections at other hospitals, but no anaesthesia produced and no improvement. Sensory root resection also attempted, with failure to produce anaethesia or benefit. Sent to me for alcohol injection. Injection of the right Gasserian ganglion by the lateral route produced total trigeminal anaesthesia and complete relief of pain.

This case is an instance of the not uncommon association of disseminated sclerosis and true trigeminal tic.

B.M., a man, aged 43 years, seen January 8, 1942. Sixteen months previously fell heavily down four steps of an air raid shelter, was taken to hospital where he remained four weeks. Has limped ever since on the right leg, and his gait has become unsteady, and the arms also. Slight bladder incontinence, marked pallor of discs. K. J., + +, and R. plantar typically extensor. All abdominal reflexes absent.

Left pupil "tonic"; at first the pupil appeared to be of Argyll Robertson type, but after being kept in a dark room for ten minutes the pupil, now larger, contracted slowly to light. C. S. F. pressure and Queckenstedt tests normal, W.R. negative, 8 lymphocytes, protein 20 mg. Lange 4333332330. Definite coarse ataxic nystagmus was present to the right side only. This is a case of disseminated sclerosis in which the question of injury to the back might be arguable medico-legally as a cause or aggravation of his disease.

The two latter cases I have chosen in order to show an unusual symptom of disseminated sclerosis in each, one with trigeminal tic, the other with a tonic pupil and a history of injury immediately preceding the commencement of symptoms.

The only reference that I have met in the literature to nystagmus resembling what I have described above occurs in Kinnier Wilson's "Neurology," 1940, vol. 1, p. 161, where he quotes Paton as describing "jelly" nystagmus as pathognomonic of disseminated sclerosis. This form may, however, certainly be met with in other conditions, and is quite different from ataxic nystagmus. Wilson goes on to say "One-sided nystagmus is by no means rare; with impaired conjugate lateral movement the outer eye sometimes shows it, or it may be more evident in that one of the two." Here I think Wilson is undoubtedly referring to ataxic nystagmus, but he evidently had not realised that it is pathognomonic of disseminated sclerosis.

I feel sure that many physicians and ophthalmic surgeons must have seen this type of nystagmus when examining cases of disseminated sclerosis, without paying attention to its peculiarity or to its special association with this form of nervous disease.

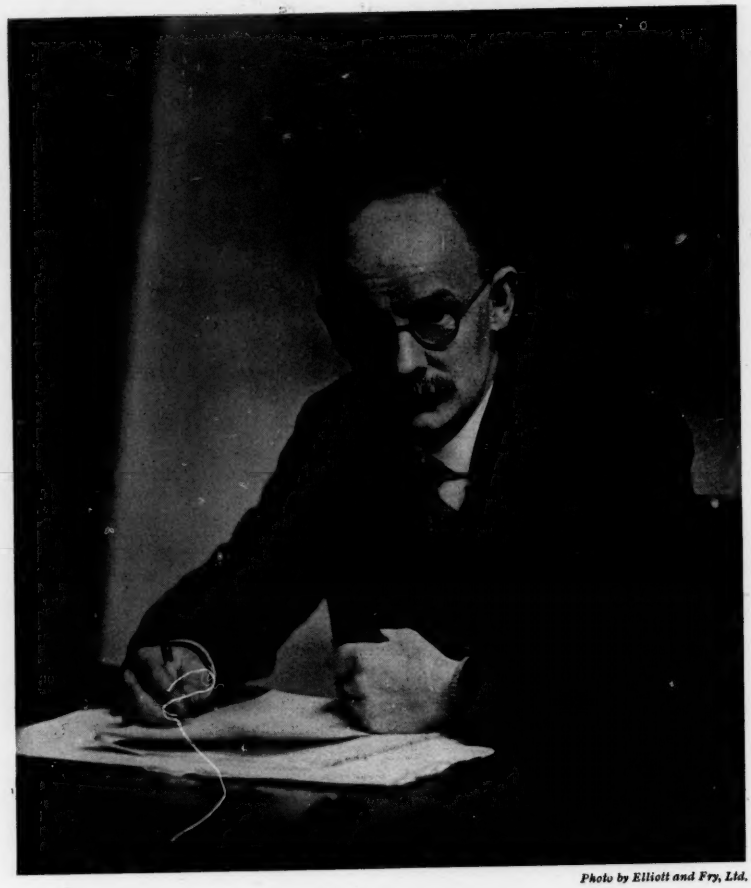

Photo by Elliott and Fry, Ltd.

ROBERT RUTSON JAMES

UNIV. of MICH.

ANNOTATIONS

Mr. R. R. JAMES

Mr. R. R. James has now occupied a post on the Editorial Staff of the *Brit. Jl. Ophthal.* for twenty years. The Directors and Editorial Committee wish to express their very great appreciation of the work which he has done, and they feel sure that the readers of the Journal will cordially agree. We all feel that we have been exceptionally fortunate in having obtained the services of so erudite and widely-read an ophthalmologist to fill the post. He has not only performed the ordinary and laborious duties of an editor with assiduity and meticulous accuracy; he has also contributed original articles on the history of ophthalmology, of which he is a past master; and his genial touch, rich in humour, must often have been recognized in many of the annotations. Special stress must be laid upon the success of the Journal during the past four years of war, when almost the entire labour of running the Journal has fallen upon his shoulders, and has been willingly borne by him. We all wish him much happiness in the future and hope that he will long continue to fill the editorial chair.

Tonometry

To an older generation, the use of a mechanical instrument for measuring the intra-ocular pressure was possibly anathema, their fingers being sufficiently sensitive to give them the required information. Ophthalmologists may now be tougher than they were and their digital pads correspondingly less sensitive, or perhaps they distrust the evidence of their senses, but be this as it may, there is an increasing tendency to use the tonometer, especially in cases where there is a doubtful rise of ocular tension or a desire to test the efficacy of some particular miotic. It is therefore timely that an article should appear in the American *Arch. of Ophthal.*, describing a "checking station" for the standardisation of these instruments, and one could wish for the institution of a similar station in this country. The principal sources of error are friction between the plunger and the sleeve, a flattened or even convex lower end of the plunger, incorrect lever ratio and a wrong curvature of the testing block, which is supplied with the instrument.

Points in applying the instrument such as seeing that it is vertical, and that the patient's eye is looking straight up, are too obvious to need comment, but the need for a careful clinical examination of the eye is not always appreciated, and resort to the tonometer may at times be too rapid. This was brought home to

the writer when he was asked to see a patient with a hazy cornea in whom the tonometer had registered the truly majestic figure of 212 mm. Hg. and immediate operation had been recommended. On examination, the case turned out to be one of old mustard gas keratitis, and the tonometer must have been applied to the surface of a protective contact lens which the patient was wearing at the time of examination, the corneal haze being due to the presence of Sattler's veil.

ABSTRACTS

MISCELLANEOUS

(1) **Estrada, A. T. (Mexico, D.F.)—Ophthalmoscopic observation of microfilarias in the vitreous of patients infected with onchocerciasis.** *Amer. Jl. Ophthal.*, Vol. XXV, p. 1445, 1942.

(1) **Estrada** describes the appearance of microfilarias in the vitreous as examined by the ophthalmoscope with a +20 to +40 dioptre lens and by biomicroscopy and the slit-lamp. He discusses the apparent differences in refringency by these methods of examination.

Of 11 cases entoptic phenomena were noted in 7. Microfilarias were found in the anterior chamber in 7 and in the vitreous in 11 cases. Conjunctival hyperaemia and photophobia were symptoms common to all cases. Punctate keratitis was present in 5 cases, perikeratitic growth in 2, iris atrophy in 1 and cataract in 1 case. The author comments that microfilarias are found in the vitreous early in the disease.

H. B. STALLARD.

(2) **Gallardo, E. and Hardy, L. H. (New York).—Virus isolated from pemphigus-like kerato-conjunctivitis.** *Amer. Jl. Ophthal.*, Vol. XXVI, p. 343, 1943.

(2) **Gallardo** and **Hardy** describe a case of severe chronic cicatrizing kerato-conjunctivitis with pannus similar in clinical appearance and course to ocular pemphigus.

They isolated from conjunctival scrapings during three different periods of exacerbation of the disease, a virus, close to if not identical with vaccinia virus. This was shown by neutralization tests in which vaccinia-immune serum neutralized the virus and the anti-virus serum neutralized vaccinia virus.

H. B. STALLARD.

(3) **Bellows, John G. (Chicago).—Local toxic effects of sulfanilamide and some of its derivatives.** *Amer. Arch. of Ophthal.*, Vol. XXX, No. 1, p. 65, July, 1943.

(3) This work was undertaken by **Bellows** because the topical application of these drugs is gaining widespread use in many branches of surgery, and because the observations on the local tissue reaction to them are both meagre and controversial. The corneae of young adult rabbits were used for the experiments, and after instillation of 4 per cent. cocaine they were rubbed with dry gauze so as to remove the epithelium—the effect being controlled by the use of fluorescein. Sulphanilamide, sulphathiazole, sulphapyridine and sulphadiazine were used in the form of a powder, a 5 per cent. ointment and a 20 per cent. suspension. The drug to be tested was applied three times daily to one eye, while the other was used as a control. There was no notable difference between the reactions produced by the four drugs, whether in the form of a powder, ointment or suspension; they all caused, not only a more than two-fold increase in the time required for epithelial regeneration, but also scarring, which was found in all the treated corneae. The scars were vascularised maculae or leucomata, and ranged in size from a few millimetres to involvement of almost the whole cornea. Noteworthy changes in the deeper layers of the cornea were absent.

Particular caution is therefore necessary in the use of the sulphonamides where the corneal epithelium has been denuded by physical or chemical injury.

F. A. W-N.

(4) **Sagher, F. and Sagher, E. (Jerusalem, Palestine).—Absorption of infra-roentgen (Bucky) rays of various qualities by the anterior portions of the eyeball.** *Arch of Ophthal.*, Vol. XXX, No. 1, p. 43, July, 1943.

(4) Beneficial results in various ocular diseases have been reported as a result of the use of these rays. The diseases are essentially those affecting the surfaces of the eyeball and lids, and include herpetic, superficial punctate, dendritic and filamentary keratatitides, also superficial infiltrations and ulcers and episcleritis. This being so, it is important to determine whether Bucky rays penetrate the eyeball in sufficient amount to produce intra-ocular complications, especially cataract, since it is well known that X-rays are apt to do this unless special precautions are taken. The **Saghers** experimented with the corneae of rabbits and of human beings, using a special instrument known as the conognom to measure the amount of rays transmitted. Their general conclusions were that with a dose of 750 r only a few roentgens would reach the lens, an amount which should easily be borne without causing pathological changes. With higher doses, *e.g.*, 5,000 r, the limit of what can be

applied to the lens is being approached, and this is also true of the ciliary body. With the softest variety of rays (half value layers of 0·02 mm. of aluminium), higher doses can be used because the penetration is only about one third of that described above.

F. A. W-N.

(5) **Hicks, Avery M. (San Francisco).—Congenital paralysis of lateral rotators of eyes with paralysis of muscles of face.** *Arch. of Ophthal.*, Vol. XXX, No. 1, p. 38, July, 1943.

(5) This condition, although first observed by von Graefe in 1875, is generally known as Möbiu's syndrome, because of his exact and detailed description of the disease in 1888 and 1892. Both eyes are affected and the principal symptoms are total paralysis of all four lateral rotator muscles or total paralysis of the abductors, with paresis of the adductors, the latter acting better in convergence than in associated lateral movements. Both facial nerves are also paralysed, either completely or partially, one side being frequently more affected than its fellow. Other congenital defects often accompany this anomaly.

The condition is probably not so uncommon as supposed, Hicks having seen no fewer than four cases of it. The first showed total paralysis of all the muscles of the face, total absence of associated lateral movements of the eyes and a weakness of convergence. The second case differed from the first in that the eyes were convergent and more or less fixed at the internal canthi; also the patient was deaf and had a supernumerary thumb and web fingers. In the third case, the facial nerve retained a few active fibres, while in the fourth, in addition to marked limitation of lateral movements, the vertical movements of the eyes also showed some restriction.

Up-to-date there appears to have been only one autopsy on a case of Möbiu's syndrome, which disclosed marked defects in the motor ganglia and nerve fibres of the medulla and pons. There were no signs of degeneration or of inflammation, and the changes were therefore ascribed to hypoplasia.

F. A. W-N.

CORRESPONDENCE

SILENT SINUSITIS

To the Editors of THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS,—I feel that the article by Miss Rosa Ford (Vol. XXVII, p. 469) on "Iridocyclitis and Choroiditis due to silent sinusitis" should not be allowed to pass without comment.

In previous correspondence (*Brit. Jl. Ophthal.*, May and June, 1942), I have ventured to criticise her contention that silent sinusitis might be responsible for "retrobulbar neuritis," by showing that silent sinusitis probably does not exist; that the cases reported were unfairly labelled retrobulbar neuritis; and that in any event there was little evidence, if any, connecting the two conditions.

These criticisms have not been answered; but Miss Ford now shifts her ground slightly and invites us to consider five cases of uveitis in only three of which she herself claims that silent sinusitis was present. I suggest that no useful purpose is served by publishing a succession of ambiguous cases without some attempt to lend verisimilitude to these "bald and unconvincing" narratives; she must first give us some valid reasons for supposing silent sinusitis to exist before discussing its effects; and secondly, she must show some probable connection between the cause and the effects.

As far as I can ascertain, this theory of silent sinusitis is founded upon the following evidence:

(1) The absence of any other feasible explanation for the reported disorders (uveitis, chronic headache, retrobulbar neuritis, rheumatoid arthritis).

I do not think it would be generally agreed that Miss Ford can claim to have excluded more orthodox explanations for many of her cases

(2) The absence of all physical signs or radiological evidence of sinusitis. This point is always stressed in her cases; in several of them a succession of eminent rhinologists have concurred in pronouncing the nose entirely normal. This evidence, to say the least, is equivocal.

(3) Contraction of the peripheral visual fields. This is the only positive finding reported before treatment, and it is, in my submission, entirely fallacious. It is almost unconfirmed. It is a physical sign of very doubtful authenticity or value. It is discounted in strong terms by those most expert in perimetry. It is not uncommon to find considerable variation in the peripheral fields of patients unaccustomed to perimetry; it is not uncommon to find contraction of the visual fields in suggestible patients. Legitimate inferences from visual field changes can be built up only as Traquair and his co-workers built them up, by the analysis of large numbers of highly skilled and laborious examinations.

(4) Post-therapeutic nasal discharge. In several of her cases much is made of nasal discharge following intranasal medication. At first sight, this appears to be a good argument, but closer inspection of the details which she herself gives shows that the reported facts actually contradict the theory. Thus she refers (*Brit. Med. Jl.*, August 1, 1942), to a profuse flow of blood and mucus "a week after the antrostomy," and (*Brit. Jl. Ophthal.*, 1942), to a mucus discharge which three weeks later contained flakes of mucopus. Surely if a hidden collection of infected material were to be drained, pus would appear immediately, and of the two, the pus would precede the mucus. These facts point much more convincingly to the production of an intranasal infection than to the relief of one.

(5) The relief of symptoms following therapy. This type of evidence is always open to the objection of "post hoc ergo propter hoc," and it is valueless unless it covers a large number of cases with adequate controls. Before relying on such evidence Miss Ford must submit a sufficiently large number of cases, and must submit evidence of controls. For example, she must submit evidence of the effects of her treatment on the normal nose. I shall look forward to her demonstration that the "normal" cases are free from silent sinusitis, which will be, on her own showing, a contradiction in terms.

ALLAN H. BRIGGS.

LINCOLN,
October 20, 1943.

NOTES

Royal Eye Hospital Clinical Society

A MEETING of the Royal Eye Hospital Clinical Society will be held at the Hospital on Friday, January 14, at 4.30 p.m., when Mr. Frederick Ridley, B.Sc., F.R.C.S. will give a talk on "The Tears."

* * * *

Royal Society of Medicine, Section of Ophthalmology

THE following dates have been arranged for the meetings of the Section of Ophthalmology of the Royal Society of Medicine.

February 11, March 31 and June 9, 1944, in each case at 5 p.m. Cases half-an-hour earlier. The March meeting it is hoped will be a joint meeting with the Ophthalmological Society of the United Kingdom.

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North of England Ophthalmological Society

MEETINGS will be held on March 4, at Liverpool, on April 22, at Sheffield and on May 13, at Newcastle-on-Tyne.

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National Ophthalmic Treatment Board

A CHANGE of fee comes into force on January 1, 1944, with regard to the National Eye Service. In future a *medical* eye examination to all insured persons, of whatever category, whether or not entitled to benefit, will be 15/-. The service will be open to any other person whose family income does not exceed £250 per annum, at the old fee of 10/6.

The arrangements as regards the cost of glasses will remain as at present.

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Special Notice

WE are asked by the Ministry of Information to state that the fact that goods made of raw materials in short supply owing to war conditions are advertised in this journal should not be taken as an indication that they are necessarily available for export.